

## Chapter 1

### • **Surgical Anatomy of the Retroperitoneum, Kidneys, and Ureters** •

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#### **Describe the layers of the lumbodorsal fascia.**

- 3 layers:
  - posterior
    - extends from spinous processes of lumbar vertebrae, covering sacrospinalis
    - most superficial to back muscles
    - latissimus extends obliquely to insert on humerus
  - middle
    - separates sacrospinalis from quadratus lumborum
  - anterior
    - passes anterior to quadratus lumborum
- all 3 layers join to form single thick aponeurosis lateral to quadratus
  - contiguous w/ aponeurosis of transversus abdominis muscle

#### **Describe the muscles of the lateral flank.**

- 3 anterolateral muscle layers
  - external oblique: most superficial
    - arises from lower ribs, goes down and anterior to insertion on iliac crest
    - free posterior border
  - internal oblique
    - originates from iliac crest and lumbodorsal fascia to extend obliquely upward and anteriorly to ribs
  - transversus abdominis
    - from lumbodorsal fascia to lateral margin of rectus sheath

#### **Where does the aorta enter and exit the abdomen?**

- enters through aortic hiatus in posterior diaphragm b/w crura
- bifurcation at lower portion of L4

#### **From superior to inferior, describe the intra-abdominal branches of the aorta.**

- inferior phrenic
  - 1st abdominal branches of the aorta
  - supply inferior portion of diaphragm, branches to ipsilateral adrenal
- celiac trunk
  - common hepatic
  - splenic
  - L gastric artery
- adrenal arteries
- SMA
  - supplies entire small bowel, most of large bowel
- renal arteries
  - lie at approximately L2 vertebral body
- gonadal arteries
  - may have single anterior trunk, or may arise from ipsilateral renal artery or aorta above renal vessels
  - pass anteriorly to ureter on either side (water under the bridge)
    - small feeder ureteric branch
  - R gonadal usually passes anteriorly to IVC
  - male: spermatic arteries
    - exit through internal ring
  - female: ovarian arteries
    - course medially into pelvis, crossing external iliac below bifurcation, enter suspensory ligament of the ovary
    - supply ipsilateral ovary and tube

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- IMA
  - arises anteriorly and to L of midline, 3-5cm above aortic bifurcation
  - usually can be sacrificed w/o complication
- common iliacs
- middle sacral artery
  - arises from terminal aorta just above bifurcation
  - extends onto anterior L5
- lumbar arteries
  - 4 pairs, occur at levels of 1st 4 lumbar vertebrae
  - course posteriorly, medial to psoas to supply posterior body wall and spine

### From inferior to superior, describe the tributaries of the IVC.

- common iliac veins
- middle sacral vein
- lumbar veins
  - more variable in number and position compared to lumbar arteries
- gonadal veins
  - L gonadal enters L renal
  - R gonadal drains obliquely into R lateral IVC below R renal vein
- renal veins
  - lie anterior to arteries
  - L renal vein longer, receives lumbar vein, L gonadal, L adrenal
- R adrenal vein: short
- L and R phrenic veins
- hepatic veins

### Describe the anatomy of the thoracic duct.

- ascending lymphatics from common iliac LN and vessels
  - follow great vessels superiorly
  - joined by lymphatics of abdominal and retroperitoneal viscera
- coalesce posteriorly to form thoracic duct
  - site of coalescence marked by localized dilation of the lymphatic chain = cisterna chyli
  - cisterna chyli lies within thorax, posterior to the aorta (or slightly to R) in retrocrural position, anterior to L1 or L2 vertebral body
  - cisterna chyli present in only 50%, variable lymphatic plexus in other 50%
- thoracic duct traverses aortic hiatus into R posterior mediastinum
- courses L at level of T4 to join venous system at junction of L jugular and subclavian veins

### What are the major lumbar nodal areas in the retroperitoneum?

- paracaval: from midline of IVC to R ureter
- interaortocaval: from midline of aorta to midline of IVC
- paraaortic: from midline of aorta to L ureter

### Describe the autonomic nervous supply in the retroperitoneum.

- Sympathetic
  - paired thoracolumbar sympathetic chains
    - arise as confluence of preganglionic fibers from T1 to L3
    - lie in groove b/w medial aspect of psoas and spine
  - connect to abdominal ganglia via greater, lesser, and least thoracic splanchnic nerves
  - synapse w/ postganglionic neurons in ganglia
    - celiac plexus
    - aorticorenal ganglion

### Describe the anatomy of the lumbosacral plexus.

- subcostal (T12)
- iliohypogastric (L1)
  - divides into lateral and anterior cutaneous branches
    - lat. branch supplies skin over the superolateral part of the buttock (area over the iliac crest)
    - ant. branch supplies skin of hypogastric region (lower anterior abdomen and pubis); supplies internal oblique and transverse abdominal muscles

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- ilioinguinal (L1)
  - passes b/w 2<sup>nd</sup> and 3<sup>rd</sup> layers of abdominal muscles and inguinal canal
  - supplies skin of scrotum (scrotal branch) or labium majus (labial branch), mons pubis, and medial thigh (femoral branch)
  - also supplies internal oblique and transversus
- Lumbar plexus (L2-4)
  - lateral femoral cutaneous (L2-3)
    - supplies skin on anterior and lateral aspects of thigh
  - femoral (L2-4)
    - supplies anterior thigh muscles
    - terminal cutaneous branch is saphenous nerve: supplies skin and fascia on anteromedial knee, leg, and foot
  - genitofemoral (L2)
    - genital branch: supplies cremaster and dartos muscles, and sensation to anterior scrotum or labia majora
    - femoral branch: supplies skin over the femoral triangle (anterior thigh below inguinal ligament)
  - obturator (L3-4)
    - ant. branch supplies adductor longus, adductor brevis, gracilis, and pectineus
    - posterior branch supplies obturator externus and adductor magnus
- Sacral Plexus (L4-S4)
  - superior gluteal (L4-S1)
    - supplies gluteus medius and minimus and TFL
  - inferior gluteal (L5-S2)
    - supplies gluteus maximus
  - sciatic (L4-S3)
    - common peroneal
    - tibial
  - pudendal (S2-4)
    - chief sensory nerve of the external genitalia
  - posterior femoral cutaneous (S2-3)
    - gives anterior sensory branch to perineum and posterior scrotum

### What is the innervation to the adrenal?

- medulla: preganglionic sympathetic fibers
- cortex: none

### What are the functions of the kidney?

- fluid balance
- electrolyte and acid-base balance
- endocrine function
  - vitamin D metabolism
  - production of renin and EPO

### Where do the kidneys lie in relation to the vertebrae and ribs?

- L kidney: T12-L3
  - upper border usually extends to upper border of 11th rib
- R kidney: L1-L3
  - R usually 1-2cm lower than L

### Describe the rotational axes of the kidney.

- 30° anterior rotation
- slight inward tilt of the upper poles
- slight anterior displacement of lower pole

### Describe the intrarenal vascular anatomy.

- Arterial
  - main renal artery divides into 5 segmental vessels
    - posterior branch: 1<sup>st</sup> and most constant
      - ◆ lies behind renal pelvis
    - apical, upper, middle, lower
  - lobar arteries
  - interlobar arteries → enter renal parenchyma

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- arcuate arteries
- interlobular arteries
- afferent arterioles to glomeruli
- efferent arterioles
- vasa recta
  - long straight vascular loops into renal medulla
- Venous
  - postglomerular capillaries drain into interlobular veins
  - arcuate veins
  - interlobar veins
  - segmental veins
    - 3-5 coalesce into renal vein
  - renal parenchymal veins anastomose freely

### What is the most common renal vessel anatomic variant?

- supernumerary renal arteries
  - artery to upper pole more common than artery to lower pole
  - lower pole arteries on R tend to cross anteriorly to IVC
  - lower pole arteries must cross anteriorly to renal pelvis: can obstruct
  - more common in ectopic kidney
- multiple renal veins: less common, usually duplicate R renal veins

### Describe the lymphatic drainage of the kidney.

- follows blood vessels through renal columns to exit renal parenchyma
- forms several large lymphatic trunks in renal sinus
- lymphatics from renal pelvis and upper ureter may join renal lymphatic trunks
- L kidney: drains to paraaortic nodes, retrocrural nodes
- R kidney: drains to paracaval and interaortocaval nodes
  - may drain directly into thoracic duct

### Describe the vascular supply to the ureter.

- Arterial
  - multiple feeding branches along its course
  - upper 1/3 in retroperitoneum: branches medially from renal artery, gonadal, abdominal aorta
  - middle 1/3: posteriorly from common iliac
  - lower 1/3: laterally from internal iliac, superior vesical, uterine, middle rectal, vaginal arteries
- Venous
  - parallel arterial supply
- Lymphatic
  - distal ureter: internal, external, common iliac LN
  - proximal ureter: paraaortic, paracaval, interaortocaval

### What are the surgical divisions of the ureter?

- abdominal: from renal pelvis to iliacs
- pelvic: from iliacs to bladder
- upper 1/3: from renal pelvis to upper border of sacrum
- middle 1/3: upper to lower border of sacrum
- lower 1/3: from lower border of sacrum to bladder

### Describe the innervation of the kidneys and ureters.

- Kidneys
  - preganglionic sympathetic input from T8-L1
  - postganglionic fibers arise from celiac and aorticorenal ganglia
  - parasympathetic input from vagus
- Ureters
  - preganglionic sympathetic input from T10-L2
  - postganglionic fibers from several ganglia in aorticorenal, superior, and inferior hypogastric plexuses







## Chapter 2

### • **Anatomy of the Lower Urinary Tract and Male Genitalia** •

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#### **What muscles make up the inguinal canal?**

- anterior wall and floor: external oblique muscle
  - folds over at inferior edge as inguinal ligament
  - edges split to form external ring
  - transverse (intracutaneous) fibers bridge the crura to form the superior edge of internal ring
- posterior wall: transversalis fascia
  - cord structures pierce this fascia lateral to the inferior epigastric vessels at internal ring
- roof: internal oblique and transversus abdominis
  - fuse as conjoint tendon, pass posterior to cord, and insert into rectus sheath

#### **What is contained in the elevations of peritoneum on the internal surface of the anterior abdominal wall?**

- median fold: overlies median umbilical ligament (urachus) → fibrous remnant of the cloaca
- medial fold: obliterated umbilical artery
  - landmark: traced to its origin from internal iliac to identify the ureter, which lies on its medial side
- lateral fold: inferior epigastric vessels

#### **What are the different layers of the pelvic fasciae?**

- outer stratum = endopelvic fascia
  - lines inner surface of the pelvic muscles
  - continuous w/ transversalis
- intermediate stratum
  - embeds pelvic viscera in fatty compressible layer
  - thickens around pelvic organs: cardinal ligament, uterosacral ligament, vesical ligaments
- inner stratum
  - lies subadjacent to the peritoneum
  - associated w/ entire GI tract
  - forms Denonvilliers' fascia

#### **What pelvic muscles insert into the perineal body?**

- superficial transverse perineal
- deep transverse perineal
- bulbocavernosus
- levator ani
- rectourethralis
- external anal sphincter
- striated urethral sphincter

#### **What are the branches of the external iliac artery?**

- inferior epigastric
  - deep circumflex iliac artery: lateral
  - pubic branch: medial
  - cremasteric branch
  - accessory obturator artery

#### **What are the branches of the internal iliac artery?**

- posterior trunk
  - ascending lumbar: supplies posterior abdominal wall
  - lateral sacral
  - superior gluteal

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- anterior trunk
  - superior vesical: gives off vesiculodeferential branch
  - middle rectal
  - inferior vesical
  - uterine
  - obturator
  - internal pudendal
  - inferior gluteal

### Describe the locations of the cavernosal nerves.

- from S2-4, pass tips of SVs
- lie within leaves of lateral endopelvic fascia new junction with Denonvilliers'
- travel at posterolateral border of prostate on surface of rectum, lateral to prostatic capsular arteries and veins
- approach prostatic capsule at 5- and 7-o'clock
- reach membranous urethra and divide into superficial branches, which travel on lateral surface of striated sphincter at 3- and 9-o'clock
- reach hilum of penis and join to form 1-3 discrete bundles, related to urethra at 1- and 11-o'clock, superficial to cavernosal veins
- pierce cavernosa to supply erectile tissue

### Describe the layers of detrusor muscle in the bladder.

- upper bladder
  - interlacing bundles loosely arranged into 3 layers
  - layers not separable
- bladder neck
  - men
    - inner longitudinal fibers
      - ◆ pass through BN to be continuous w/ inner longitudinal muscle of urethra
    - middle circular preprostatic sphincter (sphincter of the BN)
      - ◆ innervated by ++ adrenergic fibers
    - outer longitudinal fibers
      - ◆ pass anteriorly and fuse to form a loop around the BN
  - women
    - inner longitudinal fibers converge radially to be continuous w/ inner longitudinal muscles of urethra
    - middle circular layer: not robust
    - ?no outer layer
    - little adrenergic innervation

### Describe the anatomy of the UVJ.

- as ureter approaches bladder, spiral smooth muscle fibers become longitudinal
- fibromuscular sheath (of Waldeyer) starts 2-3cm from bladder and extends over ureter to trigone
- 3 layers of trigone
  - superficial layer: from ureter, extends to veru
  - deep layer: from Waldeyers sheath
  - detrusor layer: from bladder wall

### Describe the vascular supply to the prostate.

- Arterial
  - inferior vesical artery: divides into urethral artery and capsular artery
- Venous
  - periprostatic plexus
- Lymphatic
  - obturator and internal iliac nodes

### Describe the nerve supply to the prostate.

- sympathetic and parasympathetic innervation from pelvic plexus

### What is the anatomy of the external sphincter?

- signet-ring shaped, broad at its base, narrowing as it passes through the urogenital hiatus to meet apex of prostate
- fibers do not meet posteriorly → omega shaped

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- only fine, type I (slow-twitch) fibers: for tonic contraction

### What components are involved in generating closing pressure of the striated sphincter?

- pseudostratified columnar epithelium: contracts into radial folds
- submucosa: urethral sealing
- urethral smooth muscle (intrinsic sphincter)
- striated sphincter
- levator ani component

### What is the arterial supply to the testis?

- gonadal artery: branches to internal artery, inferior testicular artery, and artery to epididymal head
- cremasteric artery: from inferior epigastric
- artery to the vas: from superior vesical artery

### What is the nerve supply to the testis?

- renal and aortic plexus, travels w/ gonadal vessels
- pelvic plexus, travels w/ vas

### What is the blood supply to the labial fat pad?

- external pudendal artery  
→ can be raised on this as Martius flap

### What are the glands of Tyson?

- preputial glands present in the coronal sulcus  
→ secrete sebaceous material that constitutes smegma when mixed w/ desquamated epithelial cells

### What layers of tissue surround the penis?

- penile skin  
→ thin, no subcutaneous fat
- superficial layer of penile fascia (dartos)  
→ part of the membranous layer of the superficial fascia of the groin or perineum (Colles' fascia)  
→ contains superficial penile arteries and superficial dorsal vein: supply the skin
- tela subfascialis: very thin CT layer
- deep layer of penile fascia (Buck's fascia)  
→ heavy elastic layer that encloses cavernosae and spongiosum  
→ contains deep dorsal vein and dorsal arteries and nerves
- tunica albuginea  
→ two layers: outer longitudinal, inner circular  
→ no outer longitudinal b/w 5 and 7 o'clock, or around spongiosum

### What muscles are involved in ejaculation?

- ischiocavernosus  
→ partially encases crura of cavernosae  
→ arise from inner surfaces of ischial tuberosities  
→ increase penile turgor during erection  
→ supplied by perineal branch of pudendal nerve: S3-4
- bulbospongiosus  
→ covers spongiosum  
→ arise from perineal body  
→ innervation from deep branch in perineal nerve
- superficial transverse perineal

### Describe the vascular supply to the penis.

- Arterial  
→ Skin: superficial external pudendal → superficial penile a.  
➤ arise from first portion of femoral artery, divide into 2 main branches (dorsolateral and ventrolateral)  
➤ lies in the superficial fascia of the penis overlying Buck's  
➤ extend into prepuce: spread circumferentially and turn back to terminate near corona  
→ Deep structures: internal pudendal → common penile artery → 3 branches:  
➤ bulbourethral artery: supplies spongiosum, urethral bulb, and glans

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- dorsal artery: supplies glans mostly (few branches into cavernosae)
- cavernosal artery → gives off multiple helicine arteries
- internal pudendal → common penile + perineal artery (supplies scrotal skin via posterior scrotal artery)
- Venous – 3 systems:
  - superficial: superficial dorsal vein → L saphenous vein
  - intermediate: subtunical venular plexus (at periphery, collect blood from sinusoids) → emissary veins → circumflex veins → deep dorsal veins (w/i Buck's) + periurethral veins → Santorini's plexus → vesical plexus and internal iliac veins
  - deep: crural, cavernosal, and bulbar veins → internal pudendal veins → internal iliac vein (through Alcock's canal)
- Lymphatics
  - glans → large trunks in frenulum → traverse beneath Bucks → terminate in deep inguinal LN of femoral triangle

### What glands empty into the male urethra?

- prostate gland
- glands of Littre open into urethra along dorsal surface
  - more numerous distally and less proximally
  - form small diverticulæ: lacunae of Morgagni
- Cowper's glands (bulbourethral glands)
  - open into urethra in bulb and travel into glands located in urogenital diaphragm

### Describe the nerve supply to the penis.

- Peripheral
    - Autonomic
      - Sympathetics
        - ◆ sympathetics originate from T10/11-L2
          - ◆ pass through white rami → sympathetic chain ganglia
        - ◆ T10-T12 fibers pass through lumbar splanchnic nerves to aorticorenal ganglion and inferior mesenteric ganglion
        - ◆ L1-2 fibers pass through 3<sup>rd</sup> and 4<sup>th</sup> lumbar splanchnic nerves to superior hypogastric plexus
          - ◆ pass to superior hypogastric plexus, hypogastric nerves, then inferior hypogastric (pelvic) plexus, join w/ parasympathetics
          - ◆ go to vesical plexus, then cavernous nerves
        - ◆ responsible for detumescence
      - Parasympathetics
        - ◆ preganglionic fibers arise from neurons in intermediolateral cell columns of S2-4, pass through pelvic splanchnic nerves (nervi erigentes) to pelvic plexus (inferior hypogastric plexus) → vesical plexus → cavernous nerves
          - ◆ joined by sympathetic nerves to form ?superior hypogastric plexus
        - ◆ stimulation of parasympathetics causes erection
    - Somatic
      - thin myelinated A<sub>δ</sub> and unmyelinated C fibers originating in skin, converge to form dorsal nerve of penis
      - becomes pudendal nerve, passes under sacrospinous ligament and over sacrotuberous ligament, runs through Alcock's canal, and enters cord at S2-4
        - ◆ terminates in central gray region of lumbosacral segment
      - responsible for sensation and contraction of bulbocavernosus and ischiocavernosus
      - main cutaneous supply comes through the dorsal and posterior branches of the pudendal nerve
        - ◆ anterior scrotum and proximal penis supplied by ilioinguinal nerve
  - Supraspinal
    - medial preoptic area and paraventricular nucleus of hypothalamus and hippocampus integrate sexual function and erection
- cerebral impulses travel through sympathetics (?inhibitory interneurons to inhibit NE release), parasympathetic (to release NO and ACh), and somatic (to release ACh) to produce erection



## Chapter 3

### • Evaluation of the GU Patient •

**What points are important to elicit in the GU history?**

- HPI
  - duration, severity, chronicity, periodicity, degree of disability
  - pain
    - worse when pain causes parenchymal inflammation w/ capsular distension: epididymitis, pyelo, prostatitis
    - renal pain: usually in ipsilateral CVA lateral to sacrospinalis beneath 12<sup>th</sup> rib
      - ◆ may be associated w/ GI sx due to reflex stimulation of celiac ganglion
    - ureteral pain: usually from acute distension of ureter and hyperperistalsis and spasm
      - ◆ midureter: pain at McBurney's point
      - ◆ lower ureter: LUTS
    - bladder pain: usually intermittent SP discomfort, referral to distal urethra
      - ◆ strangury = sharp stabbing pain at end of voiding
    - prostatic pain: poorly localized → lower abdomen, inguinal, perineal, lumbosacral, rectal pain
    - penile pain: in flaccid penis, usually from bladder or urethra
    - testis pain: epididymitis or torsion, or inflammation of scrotal wall
  - hematuria
    - blood > 3 RBC / HPF is significant
    - gross or microscopic, relation to stream, painful or painless hematuria, clots, shape of clots
      - ◆ initial hematuria = urethra
      - ◆ total hematuria = bladder or above
      - ◆ terminal hematuria = BN or prostate
  - clots
    - vermiform clots: hematuria from upper tract
  - LUTS
    - obstructive sx: decreased flow, hesitancy, intermittency, PVD, straining
    - irritative sx: freq, nocturia, urge, dysuria
      - ◆ daytime frequency w/o nocturia = psychogenic
      - ◆ nocturia w/o daytime frequency = CHF/peripheral edema w/ redistribution when supine
    - incontinence
      - ◆ continuous: due to fistula, ectopic ureter
      - ◆ stress: women after birth, men after RP
      - ◆ urge: identify underlying pathology (ex: CIS, UTI, BOO)
      - ◆ overflow (aka paradoxical incontinence)
    - enuresis
  - sexual dysfunction
    - ED: psychogenic vs. organic
    - loss of libido: measure T, gonadotropins, PRL
      - ◆ amount of T needed to stimulate prostate/SV > T needed for libido → if normal ejaculate, endocrine cause unlikely
    - anejaculation
    - anorgasmia: usually psychogenic
    - premature ejaculation: usually psychogenic
  - hematospermia: usually nonspecific inflammation of prostate and SV → resolves spontaneously
    - perform external genital exam (r/o TB), PSA, DRE (r/o prostate ca), urinary cytology
  - pneumaturia: usually due to enterovesical fistula
  - urethral d/c
  - F/C
- PMHx

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- DM: autonomic dysfunction leading to impaired GU and sexual function
- TB: impairs renal function, ureteral obstruction, unexplained UTIs
- htn: sexual dysfunction due to PVD
- neurologic disease
- BOO
- sickle cell anemia → papillary necrosis, ED, priapism
- FHx
  - genetic disease: PCKD, TS, VHL, RTA, cystinuria
  - stones
  - prostate cancer
- Meds
- Smoking
  - increases TCC, PVD, ED
- EtOH
  - autonomic and peripheral neuropathies
  - impaired hepatic metabolism of estrogens → decreased T, testicular atrophy, decreased libido
- Allergies

### What are the causes of anejaculation?

- androgen deficiency → decreased secretions from prostate and SV
- sympathetic denervation
- pharmacologic agents:  $\alpha$ -agonists
- BN and prostate surgery

### What drugs are associated w/ the following GU side effects:

- decreased libido: antihypertensives, psychotropic drugs
- ED: antihypertensives, psychotropic drugs
- ejaculatory dysfunction:  $\alpha$ -blockers, psychotropic drugs
- priapism: antipsychotics, antidepressants, antihypertensives
- decreased spermatogenesis: chemo, drugs of abuse (pot, EtOH, nicotine), antiandrogens, PGs
- UI or impaired voiding: histamine, VP, Lasix, valproic acid, smooth muscle relaxants, striated muscle relaxants
- retention: anticholinergics, CCB, antiparkinsonian agents,  $\alpha$ -agonists, antihistamines
- ARF: antibiotics (aminoglycosides, pen, cephalosporins, amphotericin B), chemo (cisplatin), NSAIDs
- gynecomastia: antihypertensives (verapamil), digoxin, cimetidine, metoclopramide, phenothiazines, TCAs

### What points are important to note on the GU physical exam?

- General
  - jaundice, pallor, cachexia, obesity
  - gynecomastia
  - edema
  - lymphadenopathy
- Kidneys
  - usually not possible to palpate kidneys
  - transillumination in children < 1yr: cysts/hydro transilluminates, masses don't
  - CVAT, bruit, spinal tenderness, mass
- Bladder
  - cannot palpate if <150cc
  - tenderness
- Penis
  - phimosis, balanitis, vesicles, ulcers, masses
  - inspect inside meatus
  - urethral masses
  - hypospadias
- Scrotum and contents
  - testicular or epididymal masses, varicocele, hernia, hydrocele
- DRE: every man that presents for urologic evaluation
  - anal sphincter tone
  - prostatitis, BPH, cancer
- female pelvic exam

### Chapter 3 Questions - GU Evaluation.doc

→ cystocele, rectocele, SUI, meatus

#### What are the causes of abnormal urine colour?

- colourless: dilute urine, overhydration
- cloudy: phosphaturia, pyuria, chyluria
- red: hematuria, hemoglobinuria, myoglobinuria, beets (anthocyanin), Pb/Hg poison, phenolphthalein, phenothiazines, **rifampin**
- orange: dehydration, Pyridium, sulfasalazine
- yellow: normal, pheacetin, riboflavin (vitamins)
- green-blue: biliverdin, indicanuria, **amitriptyline**, indigo carmine, methylene blue, cimetidine, phenergan, resorcinol, **triameterene**
- brown: urobilinogen, porphyria, aloe, fava beans, rhubarb, furazolidone, **Flagyl, Macrobid**
- brown-black: alcaptonuria, hemorrhage, melanin, tyrosinosis, cascara, senna, methocarbamol, methyldopa, sorbitol

#### What is the normal specific gravity of urine?

- 1.001 to 1.035
  - < 1.008 is dilute, > 1.020 is concentrated
  - fixed specific gravity of 1.010 = renal insufficiency

#### What factors will increase or decrease urine specific gravity?

- Increase
  - decreased fluid intake, dehydration, DM, SIADH
- Decrease
  - increased fluid intake, diuretics, decreased renal concentrating ability, DI

#### What is the normal range of osmolality of urine?

- measure of amount of solute dissolved in urine
  - 50-1200 mOsm/L

#### What is the normal range of urinary pH?

- 4.5-5.5 = acidic
- 5.5-6.5 = normal
- 6.5-8.0 = alkaline
  - alkaline urine > 7.5 + UTI = urea-splitting organism (*Proteus*)

#### What factors may interfere with reliability of urine dipsticks?

- medications
  - Pyridium
  - elevated ascorbic acid levels: false -ve results for glucose and bilirubin
- excess urine on dipstick
- holding dipstick in vertical position: mixes reagents from adjacent pads
- outdated test strips
- exposure of strips

#### How does a urine dipstick test for hematuria?

- based on peroxidase-like activity of hemoglobin
- organic peroxidase substrate on strip, and hemoglobin catalyzes the reaction to cause subsequent oxidation of a chromogen indicator

#### How can one differentiate b/w hematuria, hemoglobinuria, and myoglobinuria?

- microscopic examination of spun urine
  - hematuria: large # of RBC
  - hemoglobinuria: pink supernatant, no RBC
  - myoglobinuria: clear supernatant, no RBC

#### What are the causes of false +ve hematuria readings on dipstick?

- contamination of urine w/ menses
- exercise



### Chapter 3 Questions - GU Evaluation.doc

#### What is the DDx of hematuria?

- Glomerular (dysmorphic RBC + RBC casts)
  - IgA nephropathy (Berger's disease): most common cause (30%)
  - Glomerulonephritis
    - 1°
      - ◆ Nonproliferative: minimal change, membranous, FSGS
        - ◆ should normally be inactive sediment, occasionally some hematuria
      - ◆ Proliferative: mesangial proliferative, post-infectious, RPGN (crescentic), diffuse proliferative
      - ◆ Crossover: membranoproliferative
    - 2°
      - ◆ collagen vascular disease (SLE): hx rash, arthritis
      - ◆ vasculitis (HSP)
      - ◆ Goodpasture's: hx cough, hemoptysis, bleeding tendency, microcytic anemia
  - SBE
  - sickle cell nephropathy
  - HUS
  - thin GBM disease
  - familial nephritis (Alport's syndrome): FHx hematuria, deafness
- Non-glomerular (eumorphic RBC, no casts)
  - Medical
    - hypercalciuria
    - nephrocalcinosis
    - exercise: may herald IgA nephropathy
    - cystic kidney disease (PCKD, MSK): FHx of renal cystic disease
    - papillary necrosis: in DM, blacks, analgesic abusers
    - vascular disease (renal artery thrombosis, AV fistulae, renal vein thrombosis): if hx dehydration, bruit, htn, a.fib
    - TTP
    - DIC
    - hemophilia, thrombocytopenia: FHx bleeding
  - Surgical (Post-Renal)
    - nephrolithiasis
    - cystitis
      - ◆ hemorrhagic cystitis
    - trauma
    - tumour
      - ◆ TCC: renal pelvis, ureter, bladder
      - ◆ RCC
      - ◆ hemangioma

#### What is the presentation and management of IgA nephropathy?

- Sx
  - hematuria after URTI or exercise
  - fever, skin rash
  - male predominance
  - renal insufficiency in 25%
- Ix
  - renal evaluation to r/o other causes of hematuria, GU evaluation to r/o urologic cause
    - serum Cr, CrCl, 24hr urine, renal biopsy if needed
- Tx: none

#### What factors predict for poor prognosis in IgA nephropathy?

- older age of onset
- initial abnormal renal function
- consistent proteinuria
- htn

#### What is the DDx for proteinuria?

- Isolated proteinuria
  - transient: usually resolves spontaneously, due to fever, exercise, stress

### Chapter 3 Questions - GU Evaluation.doc

- CHF in older pts
  - orthostatic: due to increased pressure on renal vein when standing
- Glomerular: tends to be nephrotic range proteinuria → suspect if 24h protein > 1g, certain to exist if > 3g
  - glomerulonephritis: 1° vs. 2° (as above)
  - DM, amyloid, arteriolar nephrosclerosis
- Tubulointerstitial: failure to reabsorb normally filtered proteins of LMW (ex: Ig) → nephrotic range proteinuria (>2-3g)
  - reflux nephropathy
  - ATIN
    - immune-mediated: sarcoid, Sjogren's, TIN-uveitis syndrome
    - drug-related: antibiotics (methicillin, pen, amp, cephalosporins, sulfa, rifampin), NSAIDs, diuretics
    - infection-related: strep, diphtheria, toxoplasmosis, brucellosis, syphilis, rickettsia, EBV
  - Fanconi's, drug/heavy metal toxicity, Balkan nephropathy, sarcoid
- Overflow
  - multiple myeloma (Bence-Jones protein)
  - hemoglobinuria
  - myoglobinuria

#### What proteins are normally found in urine?

- albumin: 30%
- serum globulins: 30%
- tissue proteins: 40% → most is TH mucoprotein

#### What can cause a false –ve dipstick reading for proteinuria?

- alkaline urine
- dilute urine
- primary protein not albumin (ex: MM)
  - if urine –ve on dip, but +ve w/ 3% sulfosalicylic acid: test for MM

#### What is the "renal threshold" for glucose absorption?

- small amounts of glucose normally excreted in urine
  - below level of detection of dipstick, not clinically significant
- if glucose filtered > 180mg/dL, exceeds absorption capacity of tubules
  - glucose detected in urine

#### How is glucose detected by a dipstick?

- glucose + glucose oxidase (on reagent pad) → gluconic acid + H<sub>2</sub>O<sub>2</sub>
- H<sub>2</sub>O<sub>2</sub> + peroxidase → oxidation of chromogen on stick, causing colour change
- specific for glucose → no cross-reactivity w/ other sugars

#### What ketones can be excreted by the kidney?

- acetone, acetoacetic acid, and β-hydroxybutyrate
  - dipstick only detects acetoacetic acid: sodium nitroprusside + acetoacetic acid → purple colour

#### What can cause a false +ve result for ketones on a dipstick?

- very acidic urine of high specific gravity
- abnormally coloured urine
- urine w/ L-dopa metabolites, 2-mercaptoethane sulfonate sodium, other sulfhydryl compounds

#### What can cause a false –ve or +ve for bilirubin on a dipstick?

- False –ve
  - presence of ascorbic acid
- False +ve
  - presence of Pyridium

#### How are WBC detected on dipstick?

- leukocyte esterase produced by neutrophils
  - catalyzes hydrolysis of indoxyl carbonic acid ester to indoxyl
  - indoxyl + diazonium salt chromogen → colour change

### Chapter 3 Questions - GU Evaluation.doc

#### What can cause a false reading for WBC on dipstick?

- False –ve
  - increased urine specific gravity
  - glycosuria
  - presence of urobilinogen
  - medications that change urine colour
  - high intake of ascorbic acid
- False +ve
  - specimen contamination

#### How are nitrates found on dipstick?

- bacteria convert nitrates to nitrites
- nitrites react w/ dipstick and undergo diazotization to form red azo dye

#### How should one obtain and prepare a urine specimen to examine the sediment?

- clean catch MSU
- 1<sup>st</sup> morning urine is best
- examine within 1hr
- 10-15cc urine spun for 5min at 3000rpm
- supernatant removed, sediment resuspended
- withdraw small amount of fluid
- pay attention to edges of cover slip: concentration of casts and other materials

#### What does one look for in urinary sediment?

- cells
  - RBC, WBC, epithelials (squamous, transitional), renal tubular cells
- casts
  - hyaline casts: made only of TH mucoprotein → no pathologic significance
  - RBC casts: diagnostic of glomerular bleeding
  - WBC casts: seen in acute GN, acute pyelo, acute AIN
  - cellular casts: nonspecific renal damage
  - granular and waxy casts: degeneration of cellular elements
    - heme-granular casts = ATN
  - fatty casts: nephrotic syndrome, lipiduria, hypothyroidism
- crystals
  - acidic urine: Ca oxalate, uric acid, cystine
  - alkaline urine: Ca phosphate, struvite
- bacteria
  - 5 bacteria/HPF > 10<sup>5</sup> CFU/mL
- yeast
  - most common seen: *Candida albicans*
- parasites
  - *T. vaginalis*: cause of vaginitis or urethritis
  - *S. hematobium*: terminal spine
- EPS
  - normal secretory granules
  - should have few, if any WBC
  - oval fat macrophages in post-infection EPS



## **Chapter 4**

### **• Basic Instrumentation and Cystoscopy •**

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#### **What are the indications for catheterization?**

- Diagnosis
  - collection for urine C&S
  - instillation of contrast
  - PVR
  - UDS
- Therapy
  - relief of BOO
  - drain after surgery
  - managing neurogenic bladder
  - stenting after surgery

#### **What are the indications for urethral dilation?**

- preparation for placement of endoscope
- therapy for urethral stricture or BN contracture

#### **What are the indications for cystoscopy?**

- diagnosis of lower urinary tract disease
  - obtaining material for cytology and histology
  - evaluation of hematuria
- access to upper tract for diagnosis and treatment

#### **What are the advantages to either the rigid or flexible endoscope?**

- Rigid
  - better optics
  - larger working channel
  - larger lumen for water flow and better visualization
  - ease of manipulation
- Flexible
  - greater comfort
  - can perform in supine position
  - can pass elevated BN easily
  - inspection at any angle

#### **What are the indications for retrograde pyelography?**

- visualize ureter or renal collecting system: if IVP inadequate
  - evaluation of hematuria
  - persisting filling defects
  - unexplained +ve cytology
  - fistulae/obstruction involving ureter





## Chapter 5

### • Urinary Tract Imaging: Basic Principles •

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#### **What should one look for on a KUB?**

- Organ outlines
  - liver, spleen, kidneys, bladder
  - displacement of normal structures
- Stomach and bowel gas
- Soft tissue abnormalities
  - flank stripe = thin layer of retroperitoneal fat b/w lateral abdo wall and intraperitoneal contents
    - displaced or enlarged by retroperitoneal fluid collections
  - psoas muscle
    - absence may indicate mass/fluid in retroperitoneum
  - soft tissue masses
- Spinal and bony pelvis abnormalities
  - spina bifida
  - sacral agenesis
  - fractures
  - mets

#### **What are the indications for IVP(EXU)?**

- hematuria
- stones
- trauma: one-shot on OR table

#### **Why are contrast agents radioopaque?**

- produced by iodine, attached to 3 of carbon atoms of benzene ring
  - triiodinated benzoic acid derivatives

#### **How can one classify contrast media?**

- high-osmolar contrast media (HOCM): monomeric ionic agents
  - most ionic contrast agents are hypertonic
    - dissociating cations of Na or methylglucamine
  - ex: Renografin, Hypaque, Conray
  - excreted by glomerular filtration
  - relative concentration of contrast increased 50-100X relative to plasma
  - mean osmotic load of 1400-2400mOs/kg H<sub>2</sub>O: 5-7X relative to plasma
- low-osmolar contrast media (LOCM)
  - nonionic monomers
    - ex: iohexol (Omnipaque), iopamidol (Isovue), ioversol (Optiray)
    - reduce osmolality by reducing # of particles in solution
  - ionic dimers
    - ex: Hexabrix, Visipaque
    - join 2 benzene rings together to increase molecular size

#### **What are the physiologic effects of iodinated contrast agents?**

- CVS
  - increased CO and decreased PVR
  - peripheral vasodilation + reflex tachycardia
  - bradycardia: direct vagal or sinoatrial node activation
- Hematologic
  - inhibition of coagulation cascade

## Chapter 5 Questions - Radiology.doc

- Renal
  - biphasic response: renal vascular dilation, then vasoconstriction w/ decrease in GFR and filtration fraction
  - osmotic diuresis

### What are the adverse effects of contrast media?

- Chemotoxic effects
  - nephrotoxic effects
    - acute impairment of renal function: increase in serum Cr by >>> or 25-50% decrease in GFR or both
    - usually nonoliguric, Cr peaks in 3-5d
- Anaphylactoid reactions
  - simulates anaphylaxis, but not mediated by Ig
  - mild (3.5% HOCM/1% LOCM): metallic taste, sensation of warmth, sneezing, coughing, limited urticaria → no treatment
  - moderate (1%/0.1%): vomiting, severe urticaria, h/a, facial edema, palpitations → may need tx
  - severe (0.09%/0.02%): hypotension, bronchospasm, laryngeal edema, pulmonary edema, LOC → life threatening, need tx

### What RF increase severity and incidence of contrast-associated renal dysfunction (CARD)?

- renal insufficiency: most consistent predictor
- DM
  - if on metformin, must hold dose for 48h → at risk for lactic acidosis if renal failure occurs
- CHF
- hyperuricemia
- proteinuria
- multiple/high doses of contrast in 24h
- dehydration
- multiple myeloma

### What RF increase risk of idiosyncratic reaction to contrast?

- hx of previous reaction
  - risk of subsequent reaction 3-4X greater
- asthma
- hx of atopy
  - hay fever and food allergies
- allergy to shellfish

### How can one decrease the risk of idiosyncratic reaction to contrast?

- pretreatment w/ steroid
  - methylprednisolone 32mg daily 1d before and 1d after test (in divided doses)
- Benadryl 50mg PO x1 before procedure
- use LOCM
- don't do study w/ contrast

### How does one treat adverse contrast material reactions?

- Benadryl PO or IV: for cutaneous reactions
- epi SC
- β-agonist inhalers: for bronchospastic reactions
- hypotensive bradycardia: due to vasovagal, treat w/ atropine
- hypotensive tachycardia: due to relative circulatory hypovolemia, treat w/ volume and pressors

### How much contrast is given for an IVP?

- 1/3-1/2 cc/lb of contrast material
  - usually 50-100cc of contrast for average pt
- rapid bolus through 18G antecubital vein

### How does one modify IVPs for the following situations:

- pregnancy
  - use US instead
  - scout + 30min post-injection film only

## **Chapter 5 Questions - Radiology.doc**

- trauma
  - intraop high-dose IVP
  - 1-2cc/lb of contrast
  - single film at 10min
- children
  - 2 post-contrast films only: 1 and 10min

### **What are the indications and contraindications to retrograde pyelography?**

- Indications
  - inadequate IVP for upper tract visualization
  - ureteral manipulations: stent placement, laser litho, biopsy
  - contraindication to IVP: contrast reaction
- Contraindications
  - UTI
  - significant obstruction: risk of bacterial seeding to upper tract

### **What are the complications of retrograde pyelography?**

- ureteral perforation
- infection
- contrast agent reaction

### **What patterns of renal backflow have been identified in retrograde pyelography?**

- Pyelotubular (aka intrarenal backflow)
  - contrast flows back into CCT
  - wedge or fan shaped area of opacification
- Pyelosinus
  - extravasation into renal sinus
  - due to overdistension of collecting system + tear in mucosa at calyces and leakage
- Pyelolymphatic
  - opacification of fine lymphatic channels in the renal hilum
- Pyelovenous
  - contrast enters venous channels

### **How can one calculate expected bladder capacity for age?**

- $[\text{age (in years)} + 2] \times 30$

### **What are the indications for cystography?**

- postop pt: exclude extravasation
- trauma: define injury

### **What are the indications for RUG?**

- urethral or pelvic trauma
- urethral strictures
- diverticulae
- fistulae

### **How does one perform a RUG?**

- place in 45° oblique position
- dependent hip acutely flexed
- 14-16F Foley placed 1-2cm inside urethra
- no lubricant
- fill balloon w/ 1-2cc water
- 10cc contrast slowly injected, film exposed

### **How does one best evaluate the posterior urethra?**

- VCUG

### **What are the complications of cystography?**

- rare



## Chapter 5 Questions - Radiology.doc

- bacteremia
- autonomic dysreflexia if high neurologic lesion

### What are the advantages and disadvantages of US in imaging the GU tract?

- Advantages
  - availability
  - flexibility
  - lack of radiation
  - non-invasive
  - accurate anatomy
  - no need for contrast
  - can determine blood flow
- Disadvantages
  - poor resolution
  - cannot see nondilated ureter and retroperitoneum
  - operator dependent
  - limited by pts body habitus
  - limited by presence of gas, ribs, surgical wounds, dressings, skin lesions

### What techniques of US are available?

- Gray-scale
  - variations in amplitudes of echoes displayed as different shades of gray
  - fluid-containing structures (cysts, dilated calyces, ureters, bladder) → absence of internal echoes, distal acoustic enhancement
  - solid tissue: speckled pattern w/ blood vessels
  - fat: highly echogenic
- Duplex Doppler
  - Doppler effect: shift in frequency of wave reflecting from moving object
  - allows measurement of velocity and direction of moving object: blood flow
- Power Doppler
  - determines amplitude of Doppler frequency shift instead of mean frequency shift
  - 3-5X more sensitive in intrarenal arteries
  - no information regarding velocity or direction of blood flow
- Contrast
- 3D

### What is the tardus-parvus waveform?

- delay in systolic upstroke downstream
- indicates RAS

### What are the indications for US of the GU system?

- Kidney
  - to gather information on #, size, shape, location of kidneys
  - detection of hydronephrosis
  - detection of solid masses
  - guiding needles for antegrade pyelogram or for NT insertion
  - assessment of renal pelvis filling defects: stones, clot, cancers, debris
  - evaluate perinephric fluid collections: abscesses, urinoma, hematoma, lymphocele
  - renal surveillance: Wilms', family screening (VHL, TS, PCKD), RCC
  - demonstrate vascular lesions: occlusion, stenosis, aneurysm, fistulae, malformations
- Adrenal
  - detection of adrenal hemorrhage
- Ureter
  - detection of hydroureter
  - demonstrate ureteric jets
- Bladder
  - measure PVR
  - for SP aspiration
  - TCC staging

## Chapter 5 Questions - Radiology.doc

- evaluate intravesical masses
- Prostate
  - for TRUS/bx
- Scrotum
  - evaluation of torsion, epididymitis, cryptorchidism, trauma, testis ca
  - demonstrate flow in cavernosal arteries

### What are the 4 phases of renal enhancement after IV contrast?

- vascular: renal arteries evaluated, 15-25 sec after IV contrast
- cortical nephrogenic: 25-80sec
- diffuse nephrogenic: 85-120sec
- excretory: 3-5min

### What are the indications for CT of the GU system?

- Kidney
  - evaluation of renal masses, enhancement
  - preoperative evaluation and staging of tumours
  - detection of perinephric abscess, urinoma, hematoma, renal infection
  - assessment of suspected renal injury and their complications
  - evaluation of retroperitoneal abnormalities: RPF
  - detection of stones
  - evaluation of renal vasculature: RAS, kidney donors, identification of crossing vessels, AV fistulae, aneurysms, before renal sparing surgery
- Bladder
  - bladder cancer staging
  - trauma: bladder rupture
- Prostate
  - evaluation of congenital anomalies, cysts, abscesses
- Adrenal
  - initial evaluation for any pt w/ suspected adrenal anomaly: Cushing's, Conn's, adrenal ca, pheo, hematoma, adenoma

### What are the average Hounsfield units for the following tissues:

- bone: +1000
- stone: > +400
- calcification: > +160
- acute hemorrhage: +50-90
- soft tissue: +10-50
- water: 0
- fat: -100
- air: -1000

### What are the CT signs for urolithiasis?

- 1°
  - presence of stone within a ureter
  - unilateral dilation of a ureter to stone w/ normal caliber below that point
- 2° signs of ureteric obstruction
  - perinephric stranding
  - hydronephrosis
  - hydroureter
  - nephromegaly

### How does MRI work?

- pt in magnetic field causes hydrogen protons to align, leading to a formation of a net magnetic vector within the pt
- applying radiofrequency pulses to the pt can cause vector to spin
- antenna outside the pt in the magnet has a current induced in it by the spinning bar magnet
- current originates in the tissues, magnitude related to the intensity of the pixel

### What are the contraindications to MRI?

- pacemakers

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- intracranial aneurysm clips
- cochlear implants
- metallic ocular foreign bodies
- older heart valve prosthetics
- obese pts: limitation to size on gantry

### What is the difference b/w T1 and T2 MRI?

- T1: measure of each protons ability to exchange energy w/ its surrounding chemical matrix  
→ is a measure of how quickly a tissue can become magnetized
- T2: measure of how quickly a tissue loses its magnetization

### What are the indications for MRI of the GU system?

- Kidney
  - differentiation of cysts from neoplasms
    - for pts that cannot receive contrast
    - indeterminate lesions on CT
  - renal neoplasms for partial nephrectomy
  - vascular lesions: suspected renal aneurysm, AV fistulae, RAS, RVT
  - visualization of RCC tumour thrombus
  - rough assessment of renal function: split and overall
  - RPF: differentiate malignant from benign
- Adrenal
  - differentiation of benign adenoma and met
  - pheo: high signal intensity on T2
- Bladder
  - differentiation b/w superficial and deep muscular invasion
  - evaluation of pts w/ SUI
  - abnormalities of female urethra: diverticulae
- Prostate
  - staging of prostate cancer
  - evaluation of young men w/ scanty or painful ejaculation, hematospermia
  - SV obstruction, stones, infection
- Scrotum
  - distinguish infection from cancer

### How can one classify radionuclides for renal scintigraphy?

- Glomerular filtration agents
  - <sup>99m</sup>Tc-DTPA (diethylenetriaminepenta-acetic acid): glomerular filtration only
    - useful for imaging blood flow and can quantify GFR
    - 20% filtered w/ each pass through kidney, 90% excreted in 24h
    - less useful in pts w/ poor renal function
  - <sup>99m</sup>Tc-GHA (glucoheptonate): glomerular filtration and cortical binding
    - handled 80-90% by glomerular filtration, rest by tubular secretion
    - some becomes fixed to tubular cells → can evaluate cortical morphology
- Renal tubular agents: better for pts w/ severe renal dysfunction
  - <sup>99m</sup>Tc-MAG3 (mercaptoacetyl triglycine): mostly tubular, some glomerular filtration
    - cleared by tubular secretion predominantly
    - can be used to evaluate renal excretory function
    - T<sub>1/2</sub> for clearance is 17min, 90% in bladder 3h after injection
    - some elimination of tracer by liver, GB, bowel
  - <sup>131</sup>I-OIH (iodohippurate): maximal tubular secretion and glomerular filtration
    - radionuclide that mostly resembles PAH (*para*-aminohippuric acid) extraction and tubular excretion
    - 10-20% handled by glomerular flow, rest by tubular secretion
    - T<sub>1/2</sub> of 30min
- Renal cortical agents
  - <sup>99m</sup>Tc-GHA
    - not as accurate as DMSA in characterizing cortical abnormalities: used if DMSA not available
  - <sup>99m</sup>Tc-DMSA
    - excreted in urine by glomerular filtration (35%) and tubular secretion (65%)

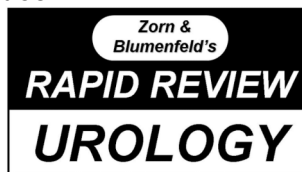
## Chapter 5 Questions - Radiology.doc

- cleared w/i 10min of injection
- higher % of cortical fixation
- acute pyelo, tubular toxicity, renal ischemia: decreased transport across cell membrane → foci of decreased activity
- Misc
  - Gallium citrate Ga 67
    - used mostly for detection of infection and lymphoma staging
    - 10-25% excreted in 1<sup>st</sup> 24h
    - accumulates in areas of infection via inflammatory protein and lysosome deposition in lymphocytes
  - <sup>99m</sup>Tc pertechnetate
    - useful to determine renal perfusion of native or transplant kidneys
- Renal transplant evaluation agents
  - <sup>99m</sup>Tc-MAG3
  - <sup>99m</sup>Tc-DTPA
    - can determine or quantify renal perfusion of allograft to r/o rejection, vascular thrombosis, or poor vascular anast
  - <sup>131</sup>I-OIH

### What are the indications of angiography of the GU tract?

- therapeutic interventions
- identify RAS or occlusion from atherosclerosis, FMD, arteritis
- trauma
- elucidation of vascular anatomy





## Chapter 6

### • Renal Physiology and Pathophysiology •

**What is the % of cardiac output that goes to the kidney?**

- 20%

**What % of plasma reaching the glomeruli is filtered into renal tubules?**

- 20%

**What are the 2 major determinants of GFR?**

- hydrostatic pressure
- osmotic pressure
  - osmotic pressure w/i Bowman's space is negligible, as there is no protein

**Why does GFR decrease if renal plasma flow decreases?**

- glomerular colloid osmotic pressure increases as fluid passes along glomerulus, due to filtration of protein-free fluid into Bowman's space
- if RPF decreases, more time for filtration across glomerular capillary, and filtration pressure dissipated more proximally along the glomerular capillary
  - $GFR = K$  (net hydrostatic pressure – net oncotic pressure)

**How does afferent and efferent arteriolar vasoconstriction affect GFR and glomerular plasma flow?**

- afferent: decreases GFR and plasma flow
  - no change in filtration fraction ( $GFR/RPF$ )
- efferent: increases GFR by increasing glomerular pressure, decreases plasma flow
  - increase in filtration fraction

**How does NO affect RBF and GFR?**

- decrease in NOS reduces RBF and GFR
- **NO is an antagonist of angiotensin II in renal hemodynamics**
- long-term NOS inhibition increases systemic BP and promotes vasoconstriction, glomerular htn, proteinuria, glomerulosclerosis

**How is GFR autoregulated?**

- as renal perfusion pressure increases, afferent arteriolar resistance increases, so glomerular pressure and GFR stable
- if BP falls, afferent resistance falls, efferent resistance increases, and GFR and RBF preserved
- mechanisms responsible for renal autoregulation not understood

**Describe the neural control of GFR.**

- kidney innervated by adrenergic neurons from the celiac plexus
- low frequency stimulation: renal sympathetic stimulation increases renin secretion, through  $\beta_1$ -adrenergic receptors on JGA cells
- increased frequency stimulation: Na reabsorption enhanced through  $\alpha$ -adrenergic receptors on PCT
- higher-frequency stimulation: GFR and RBF decreased due to increase in afferent resistance

**What is the tubuloglomerular feedback mechanism?**

- increase in afferent arteriolar resistance if there is an increase in fluid (NaCl) out of proximal tubule to the loop of Henle
  - occurs due to increased intracellular Ca in JGA cells
- negative feedback: glomerular capillary pressure inversely related to fluid delivery to distal nephron
- renin secretion decreases during TGF: allows GFR to increase and reduces reabsorption of tubular fluid

**What factors determine the magnitude of the TGF?**

*Rapid Review Urology – Study Notes (Kevin C. Zorn & Aaron Blumenfeld, 6/2006©)*

## Chapter 6 Questions - Renal Physiology.doc

- Cl content of the tubule fluid reabsorbed by macula densa cells
- osmolality of the distal tubular fluid

### What hormones act as vasoconstrictors on renal arterioles?

- angiotensin II
- NE: mediated through  $\alpha_1$ -adrenergic R
- endothelin
- vasopressin: contracts mesangial cells, not dependent on ANGII
- leukotrienes and lipoxins
- ANP
- PTH: decreases GFR by reducing  $K_f$
- epidermal growth factor

### What hormones act as vasodilators in renal arterioles?

- NO
- glucocorticoids

### What is the effect of ATII on the renal vasculature?

- stimulates vasoconstriction of the efferent arteriole (and to afferent to lesser degree)
- maintains GFR in physiologic conditions and disease states

### What are the effects of NE on the renal vasculature?

- vasoconstricts interlobular, afferent, and efferent vessels
- mesangial cell contraction
- stimulates production of vasodilator PGs (ex:  $PGE_2$ )
- stimulates renin secretion by JGA (promoting ANGII formation)

### What are the isoforms of endothelin, their receptors, and where are they expressed?

- isoforms: ET1, ET2, ET3
  - most potent renal vasoconstrictor identified
  - produced de novo by endothelial cells and by the kidney
- receptors: ET<sub>A</sub> (expressed in renal vascular smooth muscle), ET<sub>B</sub> (on endothelial cells of glomerulus and vasa recta)
  - belong to the G-coupled receptor family (PLC → IP<sub>3</sub> + DAG)

### What are the physiologic effects of ET?

- renal hemodynamic and excretory function
  - initial fall in BP and decreased renal vascular resistance
  - followed by intense systemic and renal vasoconstriction, decreased RBF, GFR, and increased BP
- effects on Na and water balance
  - decreases Na excretion

### Name an endothelin antagonist.

- bosentan

### What are the physiologic effects of LTs?

- vasoconstrictor actions similar to ANGII
  - efferent and afferent arteriolar vasoconstriction, decreases RBF and  $K_f$ , and decreases GFR

### What are lipoxins?

- AA metabolites formed by 15-lipoxygenase enzymes in PMNs
- lipoxin A vasodilates the afferent arteriole and decreases  $K_f$ 
  - increases GFR

### What are the physiologic effects of ANP?

- all serve to decrease intravascular volume
  - decrease vasopressin (ADH) release
  - decrease renin and aldo release
  - increase natriuresis
  - increase diuresis
  - decrease endothelin release

## Chapter 6 Questions - Renal Physiology.doc

- decrease vascular resistance
- efferent arteriole venoconstriction
- afferent arteriole vasodilation
- increase capillary fluid egress
- increased in CHF, but renal responses attenuated in severe CHF

### What are the 3 isoforms of NOS, and which are calcium dependent?

- all isoforms contain heme, have arginine as a substrate → NO + citrulline
  - neuronal NOS (nNOS, NOS1) – Ca dep
  - inducible NOS (iNOS, NOS2) → **iNOS calcium independent (in b/w)**
    - dependent on de novo gene expression
  - endothelial NOS (eNOS, NOS3) – Ca dep
    - stimulated by ACh, bradykinin, serotonin, others

### Where is iNOS found?

- macrophages, mesangial cells, cardiac myocytes, others

### What is the mechanism by which NO causes vasodilation?

- stimulates soluble guanylyl cyclase, increases cGMP, dilates blood vessels
- competitive inhibitors of NOS decrease NO production and are potent vasoconstrictors (L-NMMA)
- NO contributes to basal vascular tone

### What are the effects of NO on kidney function?

- decrease resistance of efferent (and afferent) arterioles
  - causes decreased glomerular capillary pressure and increases RBF
- increase Na reabsorption of PCT
- help decrease BP via NO-mediated pressure natriuresis
- potential regulator of renin secretion

### How do steroids affect GFR?

- GFR increases due to reduction in afferent and efferent resistances and related increased RBF

### What is the role of the peritubular capillaries in fluid reabsorption?

- 99% of glomerular filtrate is reabsorbed each day
  - as plasma reaches efferent arteriole, has higher osmotic pressure and decreased hydrostatic pressure than in afferent
  - net reabsorptive force at initial portion of peritubular capillary
- increase in filtration fraction will increase fluid reabsorption by peritubular capillaries
  - increased capillary oncotic pressure and decreased capillary hydrostatic pressure
  - results in decreased net urine output by PCT

### What is inulin?

- polymer of fructose – cleared solely by filtration

### How does CrCl reflect GFR?

- Cr generated by conversion from creatine and phosphocreatine
- also reflects tubular secretion, so CrCl exceeds GFR always
- assessed by collecting [Cr] from 24h urine vs. serum

### What is the Cockcroft-Gault formula?

- estimates CrCl (in cc/min)
  - $\text{CrCl} = (140 - \text{age}) \times \text{wt (in kg)} / [\text{Pcr (in mg/dl)} \times 72 \text{ (85 for women)}]$

### Where is urea synthesized?

- primarily in liver, from metabolism of dietary protein

### Where is urea reabsorbed and secreted?

- 75% excreted by kidney
  - 40-50% reabsorbed by proximal tubule, regardless of hydration
  - antidiuresis
    - large amount secreted into loop of Henle



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- large amount reabsorbed by MCT, so only 30-40% excreted
- diuresis
- neither secretion nor absorption occurs beyond proximal nephron, so urea clearance is 55-60% of GFR
- 25% metabolized to  $\text{CO}_2$  and  $\text{NH}_3$  by bowel

### What factors affect tubular handling of urea?

- Increase in fractional excretion
  - Dietary: water diuresis, high protein meal
  - Hormones: VP deficiency, glucagon, steroid, PG, SIADH
  - Other: CRF, sickle-cell
- Reduction in fractional excretion
  - Diet: low protein intake
  - Other: PG inhibition, diuretic-induced hyponatremia

### How is urea transported out of the nephron lumen?

- membrane proteins
  - UT1: in terminal collecting duct, regulated by VP
  - UT2: urea transporter of distal thin ascending loop
    - on apical and basolateral membranes
  - UT3: in RBC, vascular endothelial cells in descending vasa recta

### Where is sodium reabsorbed in the nephron?

- PCT – absorbs 60-70%
  - Na-K-ATPase in basolateral membrane, which maintains low intracellular Na level
  - Na entry is passive through Na-H antiporter → stimulated by ATII
- Loop of Henle – absorb 15-20% of filtered NaCl
  - ascending loop: Na-K-2Cl cotransporter
    - inhibited by loop diuretics [ex: bumetanide (Bumex), furosemide (Lasix), torsemide (Demadex), ethacrynic acid (Edecrin)]
    - K is recycled back to lumen fluid by ROMK channel (rat outer medulla K channel)
      - ◆ if this is blocked by ROMK blockers (sulfonylurea-type agents), lumen K decreases so much as to cause dysfunction of the Na-K-2Cl transporter → get natriuresis
- DCT – absorbs 5%
  - NaCl cotransporter
    - inhibited by thiazide type diuretics (ex: metolazone, HCTZ)
  - water impermeable
- CCD
  - principal cells: basolateral Na-K-ATPase creates electrochemical gradient
    - Na absorbed through Na channels on luminal side: blocked by amiloride, spironolactone, triamterene
    - aldosterone stimulates Na reabsorption by increasing Na entry into principal cell from lumen
      - ◆ Na-K-ATPase activity increases due to increased Na entry into cells
- MCT
  - inner MCT: through amiloride-sensitive Na channels like principal cells of CCD

### What is Bartter's syndrome?

- AR disorder characterized by volume depletion, low BP, hyperreninemic hyperaldosteronism, and metabolic alkalosis
  - salt wasting
- due to mutation in Na-K-2Cl and ROMK channels → loss of apical Na-K-2Cl function
- also have decreased Ca reabsorption in thick ascending limb → hypercalciuria

### How do thiazides affect Ca reabsorption?

- stimulate Ca reabsorption by DCT
- may activate apical Ca channels and stimulating Ca entry

### What is Gitelman's syndrome?

- variant of Bartter's syndrome
  - mutation in Na-Cl cotransporter, resulting in volume depletion + stimulation of Ca resorption
  - hypocalciuria, similar to thiazide treatment

### What are the 2 cell types in the CCD?

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- principal cells
- intercalated cells

### Describe the RAA system.

- renin converts angiotensinogen to ANGI
- ANGI converted to ANGII by ACE
- ANGII stimulates aldo release

### Where is renin synthesized?

- by JGA cells located at afferent arterioles of each nephron
  - close to macula densa cells of ascending limb of loop of Henle
- also in preglomerular circulation close to the junction of the interlobular arteries
- in postglomerular circulation in efferent arterioles

### What mechanisms regulate renin secretion?

- macula densa
  - decreased NaCl delivery to macula densa stimulates renin secretion:  $\text{Cl}^-$  dependent effect
- baroreceptors
  - increased pressure decreases renin secretion
  - decreased blood volume or perfusion pressure increase renin secretion
- neural control
  - low levels of renal sympathetic nerve activity stimulate renin secretion through  $\beta_1$ -adrenoceptors
  - increased prostaglandins increase renin secretion

### Where is ACE located?

- mostly in lungs
- on endothelial surface through vasculature
- circulates in plasma

### What are the effects of ANGII?

- vasoconstriction of efferent arteriole
  - decreased RBF
  - increased filtration fraction
  - constriction of afferent arteriole as well
- stimulates Na reabsorption (bind to  $\text{AT}_1\text{R}$  in PCT apical membrane to stimulate Na-H antiport)
  - will be natriuretic at higher levels
- decreased renin secretion
- directly stimulates aldo secretion
- stimulates thirst
- plays a role in renal development
  - ACEi cause renal development abnormalities

### What are the types of the AT receptors, and their actions?

- $\text{AT}_1$  receptors ( $\text{AT}_{1a}$  and  $\text{AT}_{1b}$  subtypes)
  - govern vasoconstriction, volume, K, and cell proliferation
  - role in renal vasculature development later in development
- $\text{AT}_2$ 
  - expressed in fetal tissue, important in renal parenchymal development early
  - role in renal function not known

### What is the role of the kidney in volume homeostasis?

- kidney maintains normal volume and BP over wide range of Na intake
- if Na intake increases, ANGII levels decrease, BP remains normal
  - renin not needed to maintain BP in high Na intake states
  - w/ constant infusion of ANGII, increased Na intake causes marked increase in BP → volume overload
- if Na intake decreases, ANGII levels increase to maintain BP
  - w/ high suppression of ANGII w/ ACEi, low Na intake causes marked drop in BP, remains normal if Na intake increases

### Where is glucose transported in the kidney?

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- proximal tubule
  - Na-glucose cotransporter: in apical mmb
    - 2 types: SLGT-1 (in outer medulla) and SLGT-2 (in outer cortex)
  - facilitated glucose and Na transport in basolateral mmb
    - glucose exits basolateral membrane via GLUT-2 transporter

### Where is K transported in the kidney?

- glomerulus
  - free glomerular filtration
- PCT – 70% reabsorbed
  - Na-K-ATPase pump in basolateral mmb
  - diffusion of K from lumen to interstitium through paracellular pathway
- loop of Henle – additional 20% reabsorbed
  - passive secretion into descending limb
  - active reabsorption in ascending limb
    - Na-K-2Cl cotransporter
    - back diffusion of K into lumen through ROMK channel
    - basolateral paths for K reabsorption: K-Cl cotransporter into interstitium, Na-K-ATPase w/ K resorption into cell
  - paracellular pathway
- DCT
  - K secreted down electrochemical gradient
- CCD
  - basolateral Na-K-ATPase pump in principal cells maintain high intracellular concentration, promoting Na absorption and K secretion
  - K secreted into lumen via ROMK channel in principal cells
  - reabsorbs K and secretes H via active exchange in A-type intercalated cells
- MCT
  - outer MCT: reabsorbs Na and secretes K via principal cells (like CCD), also has A-type intercalated cells
  - inner MCT: cannot secrete K

### What factors regulate K excretion by the kidney?

- aldosterone
- luminal sodium supply and flow rate
- diuretics
- K intake: increased K intake causes increased K secretion by CCD
- acid-base balance
- Mg balance

### How does aldosterone increase K secretion and Na absorption?

- early phase: increases apical Na channels, so Na entry into principal cells increases
  - increases Na-K-ATPase activity on basolateral mmb
- late phase: more Na-K-ATPase units added to basolateral mmb

### How does amiloride affect principal cells?

- blocks apical Na channel, abolishing aldo-stimulated K secretion

### How does licorice ingestion cause hypertension?

- cortisol and aldo bind at aldo R w/ equal affinity
  - cortisol inactivated by conversion to cortisone by 11 $\beta$ -HSD → confers tissue specificity to aldo
- glycyrrhizic acid (found in licorice) inhibits 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD)
  - 11 $\beta$ -HSD converts cortisol to cortisone, allowing aldosterone to gain access to the receptor
- cortisol stimulates mineralocorticoid R as the active steroid

### What is Liddle's syndrome?

- AD syndrome of low renin htn, hypokalemia, renal K wasting, and low levels of aldosterone
- due to genetic defect of apical Na channel in the principal cells of the CCD, causing abnormal ++ Na absorption and kaliuresis
- treat w/ amiloride → blocks Na channel

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### How does luminal Na affect K secretion?

- decreased luminal Na, kaliuretic response to aldosterone is blunted, and urinary K secretion falls
- increased Na delivery to distal nephron increases K secretion

### How does increased flow rate affect K secretion?

- increased flow rate dilutes intraluminal K, and cell-lumen gradient favours K secretion

### What diuretics are potassium wasting vs. sparing?

- K wasting
  - loop diuretics: lasix, bumetanide, torsemide
  - thiazides: HCTZ, metolazone, chlorthalidone
    - inhibit tubular reabsorption of K and Na
    - stimulate RAA system
  - carbonic anhydrase inhibitors: acetazolamide
    - increases flow rates
  - osmotic diuretics: mannitol
- K sparing
  - spironolactone, amiloride, triamterene
    - reduce K secretion by blockade of Na entry into principal cells of distal tubule and CCD

### How does acid-base status affect K secretion?

- K secretion stimulated by alkalosis, inhibited by acidosis
  - proximal RTA: hypokalemia occurs due to K secretion stimulation from increased bicarb delivery to distal nephron

### How does Mg status affect K secretion?

- renal K wasting occurs when Mg reduced
  - ex: diuretic use, EtOHism, DKA
- when hypokalemia occurs w/ decreased Mg, K replenishment cannot occur until Mg deficiency corrected

### What are the causes of hypokalemia?

- Renal loss
  - diuretics: thiazides, loop
  - aldosterone excess
  - hypertensive (any stimulus to aldo secretion)
    - primary: adrenal adenoma, adrenal hyperplasia
    - secondary: glucocorticoid-remediable aldosteronism, malignant htn, renin secreting tumour
    - nonaldosterone mineralocorticoid excess: adrenal deoxycorticosterone production, 17-alpha hydroxylase deficiency, 11β-hydroxylase deficiency
    - Cushing's: ectopic ACTH
    - adrenal carcinoma
    - licorice
    - congenital mineralocorticoid excess
  - normotensive
    - Bartter's, Gitelman's
    - RTA type I and II
  - tubulointerstitial disease
  - postobstructive diuresis
  - ATN
  - Mg depletion
  - Liddle's syndrome
  - nonreabsorbable anions: penicillin, DKA, alkali loading
- GI loss
  - diarrhea: laxatives, IBD, colon adenoma, VIP producing tumours, vomiting
  - misc: lysozymuria, dietary deficiency
- Redistribution
  - β-adrenergic stimulation
  - insulin

### What are the causes of hyperkalemia?

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- Factitious
  - lab error
  - pseudohyperkalemia: hemolysis, thrombocytosis, leukocytosis
- Increased intake
  - exogenous: diet, salt substitute
  - endogenous: hemolysis, GI bleed, catabolism, crush injury, tumour lysis syndrome
- Decreased output
  - Renal Failure
    - ARF: AIN
    - CRF
  - impaired RAA axis (decreased aldo production)
    - Addison's
    - congenital adrenal enzyme deficiencies
    - drugs: PG inhibitors, ACEi, pentamidine, beta blockers
    - hyporeninemic hypoaldosteronism
    - primary hypoaldosteronism
  - primary renal tubular K secretion defect
    - sickle cell, SLE, post-transplant, obstructive uropathy, AIN, RTA type IV
  - inhibitors of tubular secretion
    - diuretics: amiloride, spironolactone, triamterene
    - cyclosporine, Li, digitalis
- Redistribution
  - metabolic acidosis
  - insulin deficiency
  - hyperglycemia
  - aldo deficiency
  - beta blockade
  - alpha agonist
  - exercise
  - cell necrosis: rhabdomyolysis, severe hemolysis
  - resorption of large hematoma
  - periodic paralysis
  - digitalis
  - succinylcholine

### How does serum pH affect Ca binding?

- 40% of Ca normally bound to albumin, unfilterable
- as pH decreases, Ca binding to albumin decreases

### Where is Ca transported in the kidney?

- 60% filtered by glomerulus
- PCT: 65% reabsorbed
  - electrical and chemical gradients
  - active Ca-ATPase, Ca-Na exchanger on basolateral membrane
- loop of Henle: 25% reabsorbed
  - no significant absorption in thin ascending/descending limbs
  - reabsorbed in thick ascending limb
- DCT: 8% reabsorbed
  - active transport: stimulated by PTH
- CCT: small amount

### What factors affect Ca transport in the kidney?

- intravascular volume
- acid-base status
- PTH
- insulin
- glucose
- vitamin D
- Mg levels
- Ca levels

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- P levels

### How does PTH affect Ca transport?

- PTH directly stimulates Ca reabsorption by the kidney
  - occurs at proximal, loop of Henle, and distal tubule
  - active Ca transport independent of Na and water

### How does vitamin D affect Ca transport?

- kidney is major site for production of most active form of vit D (1,25-OH vit D)
- vitamin D increases renal Ca reabsorption at distal nephron

### How does ECFV affect Ca transport?

- Ca parallels Na transport
  - Ca reabsorption increased if ECFV reduced

### How do diuretics affect Ca transport?

- loop diuretics, carbonic anhydrase inhibitors, K-sparing diuretics: Ca moves w/ Na, inhibit Ca reabsorption
- thiazides: do not inhibit Ca reabsorption
  - **hypocalciuric effect, regardless of ECF volume**
  - inhibits NaCl by distal tubule, reducing intracellular Na, stimulating Na-Ca basolateral transport, enhancing Ca reabsorption

### What is the Ca-sensing receptor in the kidney?

- Ca sensing R (CaSR) identified in basolateral aspect of the thick ascending limb
- activated by high extracellular Ca, reducing renal tubular reabsorption
- also binds Mg and other ions

### Where is Mg reabsorbed in the kidney?

- as w/ Ca, occurs in thick ascending limb paralleling Na and Cl absorption
- 30% in PCT, 65% in thick ascending limb, 2-5% in DCT

### Where is phosphate excreted and absorbed in the kidney?

- 90% ultrafiltered by glomerulus
- 80-95% of filtered P reabsorbed by kidney

### What factors influence P excretion?

- PTH
  - PTH infusion causes phosphaturia
  - parathyroidectomy causes decreased P excretion
- dietary phosphate
  - amount of P excretion directly related to intake

### Where is urate reabsorbed in the kidney?

- urate filtered by glomerulus
- reabsorption in PCT
- also secreted in PCT

### What factors affect urate transport in the kidney?

- ECFV
  - urate clearance increased by volume expansion, decreased by ECF volume contraction
  - in SIADH, ECFV is expanded, urate clearance is increased, and urate levels reduced to below normal
  - in DI, ECFV reduced, and serum urate levels are high despite high urine flow rate
- Urinary pH
  - uric acid is insoluble in acidified urine
  - solubility markedly increases in alkaline pH
- Drugs
  - Hyperuricemic substances
    - Inhibition of secretion: salicylates, pyrazinamide, nicotinic acid, ethambutol, EtOH, Lasix
    - Stimulation of absorption: diuretics, chronic Pb intoxication, chronic Be intoxication
  - Hypouricemic substances

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- Inhibition of absorption: probenecid, sulfinpyrazone, salicylates, phenylbutazone, contrast, mannitol, vit C

### How does one calculate serum osmolality?

- $2 \times \text{Na} + \text{glucose} + \text{BUN}$ 
  - urea is an ineffective osmole, as it does not generate an osmotic gradient

### What are nonosmotic stimuli of thirst associated w/ decreased ECF volume?

- acute blood loss
- GI losses
- CHF
- ascites
- unilateral renovascular hypertension
- ANGII
- nausea, pain
- meds: chlorpropamide, vincristine, cytoxan, carbamazepine, clofibrate, narcotics, Haldol, fluphenazine, amitriptyline, thioridazine, NSAIDs, diuretics

### What is the countercurrent multiplier principle?

- when an exchange of material or energy occurs b/w 2 parallel columns of fluid moving in opposite directions, dissipation of energy or material is reduced
  - loops of Henle function as countercurrent multiplier that generates and maintains longitudinal solute gradient that increases in tonicity to tip of papilla

### What drugs are associated w/ water retention?

- chlorpropamide
- vincristine
- cyclophosphamide
- carbamazepine
- clofibrate
- narcotics
- haldol
- amitriptyline
- NSAIDs
- diuretics

### What happens to urinary concentration and dilution in each segment of the nephron?

- PCT
  - osmolality of glomerular filtrate identical to plasma
  - isoosmotic reabsorption of solutes in PCT and water
- Thin descending limb
  - osmolality of tubule fluid increases as it descends into medulla
  - water diffuses from lumen into hypertonic solution
  - no significant amount of active transport occurs here
- Thin ascending limb
  - only present in long-loop nephrons
  - has some diluting capacity
- Thick ascending limb
  - tubular fluid becomes more dilute as it flows back to cortex through thick ascending limb
    - hypoosmotic to plasma when it enters distal tubule
  - due to active transport of solutes out of lumen: highest Na-K-ATPase activity in kidney
  - impermeable to water
- Collecting duct
  - during water diuresis, CCD is impermeable to water and urine osmolality decreases due to ongoing Na reabsorption
  - during antidiuresis, VP increases water permeability (aquaporins) and augments Na reabsorption from aldosterone
  - terminal 1/3 of inner MCD is very permeable to urea: rapid efflux of urea into medullary interstitium
  - Water channels
    - VP binds to V<sub>2</sub>R stimulating adenylate cyclase and cAMP generation → aquaporin generation
    - gene for aquaporin mutated in congenital nephrogenic DI
- Vasa recta

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- solutes reabsorbed from loop of Henle and collecting duct diffuse from ascending to descending limbs of vasa recta and are trapped in medullary interstitium
- if medullary blood flow increases (ex: osmotic diuresis), medullary osmolality decreases and urinary concentrating ability is impaired

### How can one calculate the amount of water excreted or retained by the kidney?

- urine has 2 components
  - one that contains all solute in isotonic solution:  $C_{osm}$ , or osmolar clearance
  - another that contains only solute-free water:  $C_{H_2O}$  or free water clearance
- total urine volume (V) in L/d =  $C_{osm} + C_{H_2O}$ 
  - $C_{osm} = U_{osm} \times V / P_{osm}$
  - $C_{H_2O} = V - C_{osm} = V \times (1 - U_{osm}/P_{osm})$

### What is the most common electrolyte disturbance in patients?

- hyponatremia: defined as  $Na < 135$

### What are the causes of hyponatremia?

- osmolarity
  - most are hypo-osmolar
  - hyperosmolar: hyperglycemia, mannitol, glycerol
    - osmolality of ECF is increased by addition of impermeable solute
    - water drawn from intracellular compartment, lowering serum Na
  - isoosmolar: pseudohyponatremia, post-TURP
    - if nonaqueous phase of plasma increases (ex: hyperlipidemia, hyperproteinemia, MM)
- hypovolemic hyponatremia (water deficit + larger Na deficit)
  - thirst stimulated, VP (ADH) release occurs, and water reabsorption continues despite decreased body osmolality
  - renal losses
    - diuretic excess: usually thiazides, as they allow reabsorption of water
    - mineralocorticoid deficiency
    - salt losing nephritis
    - RTA type II
    - metabolic alkalosis
    - ketonuria
    - osmotic diuresis (glucose, urea, mannitol)
  - extrarenal losses
    - vomiting
    - diarrhea
    - third spacing
    - muscle injury
    - pancreatitis
- euvoletic hyponatremia
  - pseudohyponatremia: hyperlipidemia, hyperproteinemia, MM, DM w/ high lipids
  - glucocorticoid deficiency: aldo normal, water excretion impaired
  - hypothyroid
  - pain
  - SIADH
- hypervolemic hyponatremia: reduced effective circulating volume by baroreceptors, despite excess total body Na
  - nephrotic syndrome
  - cirrhosis
  - CHF
  - ARF, CRF
  - TURP syndrome

### What factors can impair the kidney's ability to generate solute-free water?

- GFR reduction
- inadequate delivery of filtrate to distal diluting segment
- distal diluting segment is impaired by tubulointerstitial disease or diuretics
- VP level is excessive (SIADH)



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### How do the urinary electrolytes distinguish b/w renal and extrarenal hypovolemic hyponatremia?

- renal losses: urinary Na > 20 mEq/L
- extrarenal losses: low urinary Na < 20 mEq/L = normal renal response to volume depletion

### What are the characteristic features of SIADH?

- hyponatremia w/ excretion of urine that is not maximally dilute (> 100 mOsm/kg)
- Na balance maintained so output = intake
- hypouricemia w/ plasma uric acid concentration < 4 mg/dl

### What disorders are associated w/ SIADH?

- carcinomas: bronchogenic, duodenum, pancreas, thymoma, ureter, lymphoma, Ewing's sarcoma, mesothelioma, bladder, prostate
- pulmonary disorders: pneumonia, pulm abscess, TB, aspergillosis, +ve pressure breathing, asthma, pneumothorax, CF
- CNS disorders: encephalitis, meningitis, head trauma, Guillan-Barre, SAH, SDH, cerebral atrophy, cavernous sinus thrombosis, hydrocephalus, Shy-Drager, Rocky Mountain spotted fever, DT's, MS

### What are the sx of hyponatremia?

- lethargy, N/V, seizures, coma, death

### How does one treat hyponatremia?

- increased risk of neuro complications if hypoxic, correct Na too rapidly, or increase to above 140
- correct by 1 mEq/L/hr to 125 (0.6 if chronic)
- use isotonic NS if renal or extrarenal losses
- hypertonic saline if acutely symptomatic
- calculate Na deficit =  $0.5(\text{body wt in kg})(125 - \text{serum Na})$ 
  - 0.5 is volume of distribution of plasma Na in men (0.6 for women)
- Acute (<48h)
  - emergency correction: hypertonic saline 3% at 1-2mL/kg/hr
  - give lasix
- Chronic (>48h)
  - hypertonic saline 1-2mL/kg/hr
  - give lasix
  - change to water restriction after 10% correction
  - frequent serum and urine lytes
  - ID and treat reversible causes
  - water restrict
  - demeclocycline 300-600mg bid or urea or V2R antagonist

### What is demeclocycline?

- ADH R antagonist: induces nephrogenic DI

### How does Li affect hyponatremia?

- inhibits ADH action proximal and distal to cAMP formation in CCD

### What are the causes of hypernatremia?

- Hypovolemic hypernatremia (Water and Na losses)
  - renal losses: osmotic and loop diuretics, postobstructive diuresis, intrinsic renal disease, ATN, salt-losing nephropathy
  - extrarenal losses: sweating, burns, diarrhea, fistula, bleeding, NG suction
- Euvolemic hypernatremia (Water losses)
  - renal losses: nephrogenic DI, congenital DI, hypodipsia
  - extrarenal losses: respiratory and dermal insensitive losses
- Hypervolemic hypernatremia (Na gain)
  - primary hyperaldosteronism
  - Cushing's
  - hypertonic HD
  - hypertonic NS admin
  - bicarbonate, NaCl tabs

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### What is the most common cause of central DI?

- destruction of the neurohypophysis  
→ decrease in ADH level

### What are the causes of DI?

- Genetic: X linked recessive, AR, AD
- ARF
- Electrolyte abnormalities: hypokalemia, hypercalcemia
- Systemic disorders: sickle cell, SLE, amyloid, Fanconi's, sarcoid, RTA, light-chain nephropathy
- Dietary abnormalities: increased water intake, decreased solute intake
- Meds: amphotericin B, colchicine, demeclocycline, glyburide, acetohexamide, tolazamide, lithium, methicillin, methoxyflurane, osmotic diuretics, vinblastine
- Misc: postobstructive diuresis, ATN

### How does hypercalcemia cause hyponatremia?

- causes impaired urinary concentration
  - decreased GFR w/ increased solute load per nephron
  - reduced medullary solute load from impaired NaCl absorption
  - decreased VP sensitivity from increased PGE<sub>2</sub> production
  - decreased VP-sensitive adenylate cyclase activity

### How does one diagnose and evaluate a pt w/ hyponatremia?

- measure urine osmolality
- water restriction test
  - water withheld while pts watched closely
  - measure urine volume, U<sub>osm</sub>, body weight hourly
  - measure P<sub>osm</sub> and serum Na q4h
  - then give VP and measure again

### How can one determine the cause of a patient w/ polyuria?

- urine osmolality
  - hypoosmolar (<180 mOsm/L): DI or excessive water ingestion
  - isoosmolar or hyperosmolar: look for nonelectrolyte serum osmoles (osmotic diuresis)
    - ++ osmoles → if glucosuria: DM, renal glucosuria, excessive glucose input
      - ◆ no glucose: increased urea: excessive protein intake, excessive catabolism
      - ◆ otherwise: mannitol load
    - no increased serum osmoles ( $2 \times \text{Na} + \text{K} \sim \text{Uosm}$ ) → is  $\text{Na} + \text{K} \gg \text{Cl}$ ?
      - ◆ no: diuretics, NaCl load, renal disease
      - ◆ yes: do urine pH
        - ◆ 8.0: bicarbonaturia
        - ◆ <7.0: drug anions

### How does one treat hyponatremia?

- calculate water deficit =  $[0.4 \times \text{lean body wt} \times \text{plasma Na} / 140] - 1$
- use NS if pt hypotensive → correcting hemodynamic instability takes precedence
- if normal BP, hypotonic saline may be used
- replace 1/2 deficit in 1<sup>st</sup> 24 hrs, rest over 48 hrs

### How does the body deal w/ excess acid production?

- respiratory compensation
- renal acid excretion: must reabsorb and regenerate bicarbonate

### What is the Henderson-Hasselbach equation?

- defines the bicarbonate buffer
  - $\text{pH} = 6.1 + \log [\text{HCO}_3^-] / 0.03 \text{P}_{\text{CO}_2}$
  - 0.03 = solubility of CO<sub>2</sub> in plasma
- bicarb concentration kept at 24mmol/L, P<sub>CO2</sub> fixed at 40mmHg by the lungs
- non logarithmic terms:  $[\text{H}^+] = 24 \times \text{P}_{\text{CO}_2} / [\text{HCO}_3^-]$

### How does the body deal w/ increased acid load?

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- Distribution and cellular buffering
  - initial response is distribute H ions in ECF, where buffered by bicarb
  - additional buffering occurs intracellularly in a few hrs: in bone
  - intracellular buffering requires transcellular ion transport
    - exchange H for K, can cause significant hyperkalemia
    - usually does not occur w/ organic acidoses, as H shifted into cell with organic anion, not as exchange for K
- Respiratory compensation
  - when pH decreases, chemoreceptors that control respiration are stimulated
  - alveolar ventilation increases and  $P_{CO_2}$  decreases
- Renal acid excretion
  - reabsorption of bicarb filtered by glomerulus
  - regeneration of bicarb lost in buffering acids

### Where is bicarbonate reabsorbed in the nephron?

- 80% reabsorbed in the PCT
  - $H^+$  secreted in PCT by  $Na^+-H^+$  antiporter combines w/  $HCO_3^-$ , creating  $CO_2$
  - $CO_2$  diffuses into the cell, combines w/ hydroxyl to form bicarbonate, exits at basolateral mmb via  $Na^+-3HCO_3^-$  transporter
    - catalyzed by carbonic anhydrase II
- 20% reabsorbed in distal nephron, loop of Henle, CCD (intercalated cells)
  - loop of Henle: apical Na-H exchanger +/- H-ATPase

### What are the 2 types of intercalated cells, and how does their $H^+$ secretion differ?

- Type A: H-ATPase on luminal membrane, Cl/bicarbonate exchanger on basolateral mmb
  - secretes H into lumen, bicarbonate into the blood
- Type B: similar transporters, oriented opposite
  - secretes H into blood,  $HCO_3^-$  into lumen

### What is the role of $NH_4^+$ in acid-base homeostasis?

- serves to create new  $HCO_3^-$ 
  - 2 x  $NH_4^+$  formed by deamination of glutamine → alpha-ketoglutarate
  - alpha-ketoglutarate →  $CO_2 + H_2O \rightarrow 2 \times HCO_3^-$

### How does the kidney excrete acid?

- secretion of  $H^+$  from tubule cell into lumen
- titratable acid excretion
  - filtered phosphates buffer acid
- ammonium excretion
  - PCT:  $NH_4^+$  secreted into lumen by replacing  $H^+$  on Na-H exchanger
  - thick ascending limb:  $NH_4^+$  reabsorbed by replacing  $K^+$  on Na-K-2Cl cotransporter
  - $NH_3$  then diffuses into CCD, which forms  $NH_4^+$

### What factors can affect net acid excretion by the kidney?

- luminal bicarbonate concentration
- ECF volume and body contents of K and Cl
  - decreased K will increase serum bicarbonate
  - bicarb reabsorption increases in the proximal tubule, loop of Henle, and distal nephron
  - when Cl intake restricted if K depleted, bicarb increases → similar if vomiting
- peritubular bicarbonate,  $PCO_2$ , pH
  - when bicarb and pH decrease, cell pH decreases
  - causes Na-H antiporter to work harder
- aldosterone
- AT II: stimulates H secretion
- PTH: decreases renal bicarbonate reabsorption by decreasing Na-H exchange
- neural and adrenergic effects
  - alpha receptor stimulation increases Na-H exchange in proximal tubule
  - dopamine inhibits Na-H exchange by PCT
- ANP

### How does aldosterone affect acid excretion?

## Chapter 6 Questions - Renal Physiology.doc

- Na transport from aldo promotes H excretion by making electrochemical gradient more favourable
- aldosterone may also cause increased H excretion by increasing K excretion
  - H-K-ATPase inserted into apical mmb, augmenting H secretion

### How does the kidney deal w/ an increased alkali load?

- distribution and intracellular buffering
  - large % of base remains in ECF, only 30% buffered in cells
- respiratory compensation: increases alveolar ventilation, followed by hypoventilation
  - occurs over hrs
- renal excretion
  - increases concentration of bicarbonate in glomerular filtrate
  - weakening of acidification of PCT due to alkalemia

### What is the definition of acidosis and alkalosis?

- acidosis: process that tends to elevate the blood H concentration and decrease pH
- alkalosis: process that tends to decrease blood H and raise pH

### What are the causes of a metabolic acidosis w/ an increased AG?

- lactic acidosis
- ketoacidosis: BHB
- ARF
- ingestions: salicylate, methanol, formaldehyde, ethylene glycol, paraldehyde, toluene, sulfur
- massive rhabdomyolysis

### What are the causes of a metabolic acidosis w/ a normal AG?

- Acid loads
  - ammonium chloride, TPN, DKA w/ renal ketone loss
- Bicarbonate losses
  - diarrhea, NG, pancreatic loss, ureterosigmoidostomy, meds (cholestyramine, CaCl, MgSO<sub>4</sub>), posthypocapnia
- Defects in renal acidification
  - RTA, mineralocorticoid deficiency, hyperreninemic hyperaldosteronism, mineralocorticoid-resistant hyperkalemia
- Dilutional

### How does one calculate the anion gap?

- $AG = Na - Cl - \text{bicarbonate}$
- normal = 9-14

### What are the electrolyte disturbances w/ vomiting?

- hypochloremic metabolic alkalosis
- hypokalemia
  - ECF volume decreased, stimulating renin and aldo secretion

### What is the defect in type II RTA?

- impaired reabsorption of bicarbonate in the PCT
- leads to increased excretion of bicarbonate w/ reduction in net acid excretion
- hypokalemia

### What is the defect in type I RTA?

- defect in distal acidification of urine
- metabolic acidosis occurs as kidney unable to excrete entire daily load of acid generated by the diet
- hypokalemia may occur from hyperaldosteronism

### What are the clinical features of type I RTA?

- hyperchloremic metabolic acidosis
- alkaline urine
- abnormal Ca metabolism: hypercalciuria, nephrocalcinosis, nephrolithiasis

### What are the causes of metabolic alkalosis?

- primary increase in bicarb w/ compensatory hypoventilation and increased P<sub>CO2</sub>
  - Excess Acid loss

## **Chapter 6 Questions - Renal Physiology.doc**

- nonrenal: GI fluid loss, intestinal acid loss, translocation of acid into cells (K deficiency)
- renal: persistent mineralocorticoid activity w/ K deficiency, distal Na delivery
- Excess bicarbonate gain:
  - ingestion of bicarb
  - metabolism of lactate, ketones, or other organic acids to bicarb
- Contraction alkalosis

### **How can one classify metabolic alkalosis?**

- NS (chloride) responsive
  - volume contraction
- NS unresponsive (chloride resistant): normotensive or hypertensive
  - volume expanded

### **What are the mechanisms by which the kidney eliminates waste products?**

- glomerular filtration
  - eliminates nitrogenous products of protein catabolism
- tubular secretion
  - organic acids and bases secreted
  - drugs, diuretics, antibiotics secreted
- metabolic degradation
  - filtration by glomerulus and catabolism by renal tubular cells

### **Where is EPO made in the kidney?**

- in renal cortex, by peritubular capillary cells or by peritubular fibroblasts



## Chapter 7

### • **Renovascular Hypertension and Ischemic Nephropathy** •

#### **What is the WHO definition of hypertension?**

- adults: sBP > 160mmHg or dBP > 95mmHg or both
- children: normal rise w/ age → upper normal limit 130/80 mmHg by 12-15yrs

#### **What is the definition of renovascular hypertension (RVH)?**

- htn resulting from a renal arterial lesion that is relieved by correction of the offending lesion or removal of the kidney

#### **How can one classify and characterize the various pathologic entities that cause renal arterial disease?**

- atherosclerosis (ASO): 70% of all renovascular lesions
  - usually occurs in proximal 2cm of renal artery: distal involvement uncommon
  - males, older age groups
  - progresses in 40-50%, usually in 1st 2 yrs
    - if mild (<50%) or moderate (50-75%) stenosis, most unchanged on follow-up
    - if severe (>75%) stenosis, 40% progress to complete occlusion
  - may dissect or thrombose entire vessel
- fibrous dysplasia (FD)
  - intimal fibroplasia (10% of FD)
    - circumferential accumulation of collagen inside the internal elastic lamina
      - ◆ absence of lipid seen
    - in children and young adults
    - may dissect
    - involves proximal or midportion of vessel
    - **progressive renal artery obstruction and ischemic atrophy** of the kidney always occur w/o surgery
  - medial fibroplasia (75-80% of FD)
    - usually in women aged 25-50yrs
    - often bilateral, can involve other vessels (carotid, mesenteric, iliac)
    - much of muscle replaced by collagen: can thin or cause aneurysms
      - ◆ aneurysms large, absence of extreme collateral circulation
    - **"string of beads"** on angio in distal 2/3 of main renal artery and branches
    - rarely see decreasing renal function, dissection, thrombosis, or rupture
    - seldom have progression after age 40
  - perimedial fibroplasia (10-15% of FD)
    - young women aged 15-30 → **aka "girlie disease"**
    - occurs only in renal artery
    - tightly stenotic lesion enveloping entire renal artery
    - collagen deposited in outer media, confined to external elastic lamina, just beneath adventitia
    - may see arterial beading
    - frequently see extensive collateral circulation (vs. none w/ medial FD)
    - progression w/ renal atrophy occurs in all pts managed nonoperatively
  - true fibromuscular hyperplasia (rare: only 2-3% of FD)
    - diffusely involves media
    - seen in kids and young adults
    - only renal artery disease w/ true hyperplasia of smooth muscle cells
    - appears as smooth stenosis of renal artery: identical to intimal FD
- miscellaneous
  - RAA, middle aortic syndrome, periarterial fibrosis, post-traumatic disease

#### **Where is angiotensinogen produced?**

- primary site of production is liver

## Chapter 7 Questions - RVH.doc

- not stored: secreted directly after production
- production is stimulated by estrogens, steroid, stress (infection, tissue injury), RAAS system feedback

### Where is renin produced?

- kidney is major site of renin production
  - also found in other tissue

### What mechanisms affect renin secretion?

- Stimulation of renin secretion
  - Macula densa mechanisms
    - reduction of distal tubule salt delivery (chloride concentration)
  - Baroreceptor mechanisms
    - decreased cell stretch from renal hypoperfusion
  - Neural mechanism
    - stimulation of  $\beta$ -adrenergic nerves
    - dopamine
  - Endocrine and paracrine mechanisms
    - PGE<sub>2</sub> and PGI<sub>2</sub> (prostacyclin), and exogenous arachadonic acid
  - Intracellular mechanisms
    - agents that increase adenylate cyclase:  $\beta$ -adrenergic stimulation, PGE<sub>2</sub>, PGI<sub>2</sub>, dopamine, histamine, PTH
  - Disease states
    - steroids, thyroid hormone, silicosis, PBC, sarcoid
- Inhibition of renin secretion
  - ANGII, endothelin, VP, ANP

### Where is ACE found in the body?

- lung, kidney (glomerular epithelial cells), ileum, duodenum, uterus, CNS, adrenal, testes, prostate, fallopian tube
- primarily expressed on endothelial, epithelial, and neuroepithelial cells
- circulating ACE: endothelial cells and macrophages

### What are the physiologic effects of ANGII?

- Renal
  - General
    - vasoconstriction and release of aldo
    - vascular growth
  - Glomerular
    - increase in efferent arteriolar resistance, smaller increase in afferent resistance (if increase in RBF)
    - mesangial cell contraction
    - overall will maintain GFR
  - Tubular
    - increase in filtration fraction will increase osmotic pressure in postglomerular vessels, leading to increase in fluid reabsorption
    - low levels stimulate Na absorption in PCT, higher levels inhibit Na transport
  - Medullary
    - decreases medullary blood flow → increased medullary hypertonicity and concentration of urine
- Vascular
  - increases BP by increasing PVR: direct contractile effect on vascular smooth muscle cells
  - stimulates vascular smooth muscle growth
- Adrenal
  - acts directly on adrenal glomerulosa to produce aldo secretion (from corticosterone)
- CNS
  - increase in drinking and salt appetite
  - increased secretion of CRH, PRL, LH, oxytocin, VP
- Gonadal
  - function unknown

### Where are ANGII R located in the body?

- AT1a: liver, adrenal, kidney, aorta, uterus, ovary, spleen, lung, hypothalamus

## Chapter 7 Questions - RVH.doc

- AT1b: liver, adrenal, kidney, uterus, pituitary
- AT2: in fetal life, present in adrenal, kidney, liver, skin, tongue, brain

### Describe the classic one-clip models of RVH.

- 2 kidneys, 1 clip
  - renal artery to one kidney is clipped
  - RAAS activated due to renal ischemia and hypoperfusion
  - generalized vasoconstriction and systemic hypertension
  - 2<sup>o</sup> hyperaldosteronism and Na retention by stenotic kidney
  - contralateral kidney sees higher-than-normal perfusion pressure, reacts by suppressing renin secretion
    - works against other kidney, prevents systemic BP from reaching high levels to suppress stenotic kidney
  - unclipping, ACEi, ANGII antagonists: marked decrease in BP
  - overall: euolemia and htn
- 1 kidney, 1 clip
  - one kidney is clipped, other kidney is removed
  - solitary ischemic kidney secretes renin, activating RAAS
  - stenotic kidney conserves Na and water, producing volume expansion
  - elevation of BP, Na retention gradually suppress renin secretion

### What are the different phases of renovascular hypertension?

- Acute
  - renin dependency
- Transitional
  - progressive volume and Na retention
  - gradual onset of secondary hyperaldosteronism
  - thirst
  - progressive suppression of renin secretion
  - progressive decline of contralateral natriuresis
- Chronic
  - volume expansion
  - suppressed renin secretion
  - systemic vasoconstriction
  - increased sensitivity to ANGII
  - increased VP secretion
  - increased sympathetic activity
  - structural vessel wall changes
  - development of contralateral nephrosclerosis

### What is ischemic nephropathy (IN)?

- deterioration of renal function due to chronic hypoperfusion of the total functioning renal mass
  - ex: bilateral RAS, stenosis of solitary kidney
- injury not due to cell death due to lack of oxygen, as oxygen demand < supply
- reduction in RBF causes IN without causing renal death
  - flow rate exceeds need of kidney for oxygenation, but is necessary for glomerular filtration

### What are the structural changes in the chronically ischemic kidney?

- tubular changes: patchy tubular necrosis and atrophy
- decreased glomerular size
- glomerular sclerosis
- hypercellularity of the JGA
- arteriolar thickening and hyalinosis
- cholesterol microemboli within the renal vasculature → poorer prognosis

### What are the RF for renal atheroembolism?

- older hypertensive pts
- severe abdominal aortic ASO

### What is the etiology of renal cholesterol embolism?

- spontaneous



## Chapter 7 Questions - RVH.doc

- following manipulation of the atherosclerotic aorta: surgery, angio, thrombolytic agents

### What is the management of cholesterol emboli to the kidney?

- prevention
  - avoid unnecessary/rough manipulation of atherosclerotic vessels
  - avoid prolonged anticoagulation in pts at risk
- supportive
  - removal of inciting trauma
  - cessation of anticoagulants
  - control htn
  - start renal replacement therapy prn

### What are the clinical features of RVH?

- Hx
  - age of presentation: < 30 yr, > 55 yr
  - no FHx htn
  - sudden onset, short duration of htn
  - difficult to control htn
  - accelerated malignant htn or hypertensive crises
  - htn associated w/ pulmonary edema, generalized atherosclerotic disease, gradual impaired renal function
  - smoking
- P/E
  - severe htn
  - upper abdominal/epigastric bruit
  - severe hypertensive retinopathy
  - generalized atherosclerosis
- Labs
  - mild proteinuria
  - azotemia
  - hypokalemia: due to activation of RAAS

### What RF are associated w/ presence of ARAS?

- higher age
  - older pts w/ poor renal function w/ no obvious cause
- female gender
- hx CHF
- atherosclerosis
  - AAA
  - CAD
  - PVD
  - aorto-occlusive disease
  - lower extremity occlusive disease
- DM
- elevated Cr
- progressive azotemia after medical control of BP
- **htn not predictive for presence of ARAS**

### Why does control of BP decrease renal function in pts w/ RAS?

- perfusion-dependent renal function
- $\beta$ -blockers cause a fall in CO
- ACEi lead to loss of efferent arteriolar vasoconstriction tone in the kidney

### What populations should be screened for ARAS?

- older pts w/ most or all of:
  - generalized atherosclerosis
  - decreased size in one/both kidney/s
  - renal insufficiency (even mild)
  - progressive azotemia after BP control
  - CAD

## Chapter 7 Questions - RVH.doc

- hx CHF
- PVD
- **presence of htn should not influence decision to screen**

### What studies can be used to diagnose RAS?

- IVP
  - a.k.a. hypertensive, rapid-sequence or minute sequence urogram
    - series of quick films q1min after injection, no abdo compression
  - poor sensitivity and specificity
  - not useful to assess bilateral lesions: can only compare sides
- peripheral PRA
  - designed to diagnose overactivity of RAAS
  - no anatomic value, cannot diagnose IN
  - hold antihypertensives for 2 weeks, standardize test
  - 16% of pts w/ essential htn have increased PRA, 20% of pts w/ RVH have normal PRA
- captopril test
  - measure PRA before and after PO dose of captopril
  - after ACEi, pts w/ RAS have higher rise of PRA than pts w/ essential htn
  - standardization: can take  $\beta$ -blockers, stop diuretics and ACEi 1 week prior, normal/high salt diet needed, blood taken w/ pt in same position, PO dose 25mg captopril, take 2nd dose 1hr after ACEi
  - criteria for +ve test
    - post captopril PRA > 12ng/cc/hr
    - absolute increase in PRA > 10ng/cc/hr
    - 400% increase in baseline PRA (150% increase if baseline > 3ng/cc/hr)
  - not reliable in pts w/ azotemia, children
  - low sensitivity, not useful for screening
- renal vein renins
  - renin secretion by kidney = RVR - arterial renin (which approximates IVC renin)
  - hypersecretion of renin from ischemic kidney (>50% PRA) confirms RVH
  - contralateral suppression of renin secretion (RVR = IVC renin) is normal response
  - can sample segmental renal veins to localize segment (if RVR < 50%)
  - used generally to determine the more ischemic kidney in bilateral RVH
- captopril renography
  - ACEi causes decreased GFR for kidney distal to stenosis: measured by radionuclide renography
  - standardization: well hydrated pt, liberal salt intake, d/c ACEi for 3-5d, continue other antihypertensives, PO captopril 25-50mg
  - captopril renogram taken first, baseline study taken next day
  - usually use DTPA, OIH, or MAG3
  - observe symmetry of renal size and function, and specific captopril-induced changes
  - sens/spec 90-93% / 93-98%
- duplex US
  - uses real-time B-mode US to obtain blood flow velocities in major abdominal vessels
  - flow velocity at renal hilum and inside parenchyma measured
  - sens/spec 98%
- MRA
  - sens/spec 93%/90%
- CTA
  - 2mm slices during single breath
  - cannot define disease distal to main renal artery, but can see accessory vessels
  - need large amount of IV contrast
  - sens/spec 90%/97%
- arteriography
  - gold standard

### What are the findings on IVP suggestive of RVH?

- delayed appearance of contrast
- disparity of renal size > 1.5cm
- delayed hyperconcentration
- retention of contrast in nondilated collecting system

## Chapter 7 Questions - RVH.doc

- notching of pelvicalyceal system by collateral vessels

### What are the findings on captopril renography suggestive of RVH?

- delayed time to max activity (>11min)
- marked cortical retention of radionuclide
- marked decrease in GFR of affected kidney
- poorly functioning kidney w/ no change after captopril
- bilateral symmetrical change after ACEi

### What are the findings on duplex US characteristic of RAS?

- altered flow pattern distal to stenosis
- turbulent jet during systole and decrease in diastolic flow
- peak systolic velocity (PSV) > 180cm/sec
- ratio of renal PSV to aortic PSV = renal aortic ratio (RAR)
  - RAR > 3.5 indicates severe RAS (>60%)

### What are the advantages and disadvantages of duplex US?

- Advantages
  - noninvasive
  - portable equipment
  - inexpensive
  - widely available
  - no contrast or radiation
  - no effect on renal function
  - renal function (azotemia) has no effect on test outcome
  - no discontinuation of antihypertensives
- Disadvantages
  - operator dependent
  - difficult to see renal artery in obese pts, pts w/ ++ gas
  - no functional data: anatomic only

### What are the advantages and disadvantages of MRA in diagnosing RAS?

- Advantages
  - noninvasive
  - no contrast or radiation
  - low technical failure rate
  - can obtain functional data: RBF, GFR
- Disadvantages
  - image quality inferior to angio
  - cannot use in pts w/ magnetic implants, claustrophobia
  - not widely available

### What are the disadvantages of contrast arteriography?

- invasive test, requires arterial puncture and manipulation of arterial catheters
- expensive, cannot be done as outpt
- involves contrast and radiation

### What are the complications of arterial puncture and manipulation?

- bleeding
- hematoma
- dissection
- thrombosis
- distal embolization of disease
- allergic reaction to contrast
- volume overload
- transient impairment of renal function

### What are the advantages of CO<sub>2</sub> arteriography?

- cleared by lungs w/o adverse effects

## Chapter 7 Questions - RVH.doc

- nonallergenic
- cheap
- no problems w/ fluid overload
- smaller catheters: minimal trauma to arterial walls

### How does one determine the appropriate study to diagnose RAS or RVH?

- RAS
  - strong suspicion: arteriography straight away
  - mild-moderate suspicion: non-invasive test → DUS, MRA, CTA
    - depends on renal function
- RVH
  - functional evaluation of RAAS before anatomic study
  - strong suspicion: arteriography
  - low-moderate suspicion: captopril renography
    - if not satisfactory, perform another noninvasive test

### What factors determine if a pt requires surgical revascularization for renovascular disease?

- RVH
  - type of disease
    - medial fibroplasia: initial tx is medical management of htn
      - ◆ loss of renal function is uncommon
    - intimal or perimedial FD: require early interventional tx
    - atherosclerotic RVH: aggressive medical management → older pts, often have extrarenal vascular disease
  - angiographic findings
    - main renal artery stenosis: angio has excellent results
    - branch renal artery: increases technical difficulty of PTA → need surgical renal revascularization
- IN
  - anatomic severity and extent of renal artery disease
    - if disease poses severe threat to overall renal function
      - ◆ high-grade stenosis (>75%)
      - ◆ bilateral disease
      - ◆ solitary kidney
    - if contralateral kidney normal, revascularization not needed purely to preserve renal function
  - level of renal function
    - revascularization useful only if not yet severe, permanent impairment of renal function
    - not worthwhile if severe azotemia
  - rate of decline of renal function
    - rapid decline suggests strong possibility of salvage
    - pts w/ ESRD and ARAS w/o complete occlusion cannot be salvaged
  - renal histopathology
    - intact glomeruli on bx indicate possible salvage
      - ◆ tubular atrophy, interstitial fibrosis, arteriolar sclerosis → lesser importance
    - widespread glomerular hyalinization = no possibility of salvage

### What clinical clues reveal if a kidney w/ complete arterial occlusion is salvagable w/ renal revascularization?

- angiography w/ retrograde filling of distal renal artery tree
- renal bx w/ well preserved glomeruli
- kidney size > 9cm
- function of involved kidney on renal scan or IVP

### What are the results from surgical revascularization for renovascular disease?

- RVH
  - increased risk of operative mortality w/ bilateral simultaneous renal revascularization, or w/ other major vascular OR
  - FD: minimal operative morbidity and mortality (2-6%)
    - 50-60% cured, 30-40% improved, <10% failure rate
  - atherosclerotic RVH
    - 15-40% cured, 50-70% improved, 10-20% failure rate
    - higher failure rate due to superimposition of RVH on essential htn in these older pts

## Chapter 7 Questions - RVH.doc

- atherosclerotic IN
  - 50% improved, 30-40% stable, 10-20% deteriorate

### What factors correlate w/ poor long-term survival post-revascularization for ARAS?

- age > 60
- CAD
- previous vascular operations

### What is the role of secondary renal revascularization?

- controversy concerning if previous PTA increases difficulty or compromises outcome
- after surgical revascularization, recurrence of RAS usually late complication
  - if involved kidney is salvagable, attempt to restore normal arterial flow
  - scant experience w/ PTA post surgical revascularization

### How does one deal w/ 2 renal arteries originating in close proximity from aorta?

- kissing balloon technique
  - dilation of one vessel may occlude other
  - diagnostic catheter placed into uninvolved artery
  - if lumen compromised, exchange for 2<sup>nd</sup> balloon

### What is the mechanism through which PTA increases arterial diameter?

- fracture of the atherosclerotic plaque
- stretching of the arterial wall w/ intimal tearing also occurs

### What are the complications of PTA?

- complications related to arterial puncture
- complications related to use of contrast
- specific complications from manipulating renal arteries
  - transient deterioration of renal function
  - dissection/thrombosis of renal artery
  - renal artery rupture

### What are the results of PTA for renovascular disease?

- RVH
  - FD: measures of success are quite variable, most studies combine FD and ASO pts
    - usually performed w/o stent placement, success in 80-90%, failed in 10-20%
    - cure of htn in 80-100%
  - ARAS: pattern of arterial disease usually bilateral and ostial, pts generally older, generalized PVD
    - less successful for BP: cure rate 15%, improved in 50-60%, failed in 30%
    - restenosis rates of 8-22% (35% in ostial lesions)
    - major complications in 5-24%, mortality 1-2%
    - effects on renal function: improved in 15-40%, stabilization in 25-50%
- inflammatory RAS
  - Takayasu's arteritis: successful dilation in 90%, restenosis in 20%, 50% cured of htn

### What are the indications for stent placement at time of PTA?

- poor immediate results from PTA alone
- restenosis after PTA
- treatment of angioplasty complications
- lesions in which PTA alone unlikely to be successful: ostial lesions in ARAS

### What are the results after stent placement for RAS?

- technical success >95%
- restenosis 6-38%
  - usually occurs due to hyperplastic intimal reaction
  - higher patency rates w/ stent vs. PTA alone
- BP response
  - cured in 15-30%, improved in 40-70%, same in 25-50%
  - low cure rates due to concomitant essential htn and renal parenchymal disease

## Chapter 7 Questions - RVH.doc

- renal function response
  - improvement in 15-60%, stable in 25-75%

### What are the complications of endovascular stenting?

- not much different from PTA alone
  - complications of renal PTA
    - higher incidence of access site complication due to larger arterial puncture required
    - higher incidence of contrast nephropathy due to larger contrast load needed
  - complications of stent delivery
    - endovascular infection
    - mycotic aneurysm
    - death

### What are the different types of renal artery aneurysms?

- saccular: most common (75%)
  - generally occur at bifurcation: ?inherent weakness at this point
  - bilateral in 25%
  - incomplete calcification: soft, thin, and ulcerated b/w zones of Ca → predisposed to rupture
  - may erode into renal vein
- fusiform
  - occur as a uniform dilation of entire segment of renal artery
    - post-stenotic dilation
  - generally no calcification
  - young, hypertensive pts w/ stenosing fibrous renal arterial disease
  - thrombosis of involved arterial segment from progressive stenosing vascular disease
- dissecting
  - results from tear in internal elastic membrane of renal artery
  - intima separated from media
  - may re-enter lumen later to preserve renal function
  - usually complications of renal arterial involvement w/ ASO, intimal FD, or perimedial FD
- intrarenal
  - etiology: congenital, post-traumatic, iatrogenic, neoplastic, PAN
  - propensity to rupture
  - post-trauma: may resolve spontaneously

### How can one diagnose a RAA?

- Hx/Px
  - usually asymptomatic
  - htn, subcostal/flank pain, hematuria, abdominal bruit, palpable pulsating mass
  - RVH in 15-75%
- Ix
  - ringlike calcification in or near the renal hilum on KUB

### What are the complications of RAA?

- peripheral dissection
- arterial thrombosis w/ renal infarction
- emboli
- obstructive uropathy
- erosion into vein w/ AV fistula
- spontaneous rupture

### What factors predispose to RAA rupture?

- absent or incomplete calcification
- aneurysm size > 2cm
- coexisting htn
- pregnancy

### What are the indications for repair of a RAA?

- renal ischemia and htn

## **Chapter 7 Questions - RVH.doc**

- dissecting aneurysm
- local sx: pain, hematuria
- woman of child-bearing age
- presence of significant RAS
- expanding size on serial imaging:
  - absolute size > 2cm
- thrombus detectable on angio w/ evidence of distal embolization

### **How can one classify renal AV fistula?**

- congenital (25%)
  - cirroid or angiomatous configuration w/ multiple communications
  - appearance on angio
    - multiple small interconnecting arterial and venous channels
    - impaired distal renal parenchymal vascularity
    - early filling of renal vein
  - M:F 1:1
- idiopathic (3-5%)
  - single, not cirroid, no apparent cause
- acquired (70-75%)
  - appear as solitary communication b/w artery and vein
  - most common cause: iatrogenic trauma from renal bx

### **What are the causes of acquired renal AV fistula?**

- renal biopsy
- RCC
- blunt/penetrating renal trauma
- inflammation
- renal surgery

### **What are the clinical manifestations of renal AV fistula?**

- abdominal bruit: usually loud and high pitched
- CHF
- cardiomegaly
- diastolic htn
- hematuria
- tachycardia
- palpable flank mass: from spontaneous rupture

### **What is the tx of renal AV fistula?**

- RCC: nephrectomy
- most usually close spontaneously: after renal bx, 70% close in 18mo
- transcatheter angiographic occlusion
- total or partial nephrectomy

### **What are the indications for tx of renal AV fistulae?**

- htn
- CHF
- severe hematuria
- angiographic evidence of expanding lesion
- rupture
- progressive renal failure

### **What are the causes of renal arterial thrombosis and embolism?**

- Renal artery thrombosis
  - blunt/penetrating trauma
  - angiography
  - atherosclerosis
  - FD
  - PCV

## Chapter 7 Questions - RVH.doc

- umbilical artery catheterization
- inflammation of renal artery: syphilis, polyarteritis, thromboangiitis obliterans
- Renal artery embolism
  - SBE
  - aseptic cardiac valvular vegetations
  - CABG
  - a fib
  - saccular RAA
  - cardiac tumour
  - acute MI
  - ventricular aneurysm
  - "paradoxical" embolism: clot originating in venous system, passes through ASD/VSD to arterial system

### Where does thrombosis/embolism usually occur in the kidney?

- thrombosis: usually in proximal/middle 1/3 of main renal artery
- embolization: peripheral arterial branches

### Why is acute arterial occlusion more common on the left?

- more acute angle b/w L renal artery and aorta

### What are the clinical manifestations of RAT/RAE?

- dull aching abdo/flank pain
- N/V, F/C
- htn
- albuminuria
- microhematuria
- leukocytosis
- increased LDH

### What is the tx of RAT/RAE?

- traumatic: do not attempt surgical revascularization if N contralateral kidney
- can attempt percutaneous streptokinase or TPA
- renovascular reconstruction if bilateral or solitary kidney

### How does neurofibromatosis affect the renal arteries?

- RAS + htn
- arterial stenosis seen in origin or proximal 1/3 of main renal artery
- renal revascularization is tx of choice for associated RVH

### What is middle aortic syndrome?

- nonspecific stenosing arteritis affecting the aorta and its major branches including renal arteries
  - is a form of Takayasu's arteritis
- autoimmune disease
- inflammation does not extend to iliacs
  - tx w/ autotransplantation

### What are the causes of extrinsic renal artery obstruction?

- neural tissue, musculocutaneous fibers, diaphragmatic crura
- inflammation, trauma, tumour, prior rads

### What is Page's kidney?

- kidney compressed by subcapsular or perirenal process causing renal ischemia
- induces unilateral stimulation of RAAS and contralateral suppression

### What are the causes of Page's kidney?

- blunt trauma
- closed renal biopsy
- anticoagulation
- hemorrhage from a tumour



## **Chapter 7 Questions - RVH.doc**

### **How does one dx Page's kidney?**

- presence of surrounding hematoma or encasing fibrous pseudocapsule on CT, MR, US

### **What is the tx of Page's kidney?**

- medical tx for htn
- percutaneous evacuation of hematoma
- open drainage of hematoma
- nephrectomy

### **What renal parenchymal disorders can cause htn?**

- chronic pyelo: segmental scars
- hydro
- congenital hypoplasia or dysplasia
- segmental hypoplasia (Ask-Upmark kidney)
- VUR
- RCC
- benign cyst
- Wilms' tumor
- radiation nephritis
- JGA tumor



## Chapter 8

### • Etiology, Pathogenesis, and Management of Renal Failure •

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#### **What is the definition of ARF?**

- rapid reduction in renal function characterized by progressive azotemia that may or may not be accompanied by oliguria
- results in failure to excrete nitrogenous wastes or to maintain N volume and electrolyte homeostasis
- cardinal feature of ARF is decreased GFR

#### **What can increase the BUN?**

- marked volume contraction
- hypercatabolic states
- marked increase in protein load
  - GI bleed
  - TPN

#### **How can one classify the etiology of ARF?**

- Prerenal
  - Volume depletion: systemic hypotension
    - Surgical losses: hemorrhage
    - GI losses: N/V, diarrhea, fistulae
    - Renal losses: overdiuresis, salt-wasting d/o
  - Cardiac causes: primary decrease in CO
    - Acute: MI, arrhythmias, malignant hypertension, tamponade, SBE
    - Chronic: valvular disease, chronic CM
  - Redistribution
    - Hypoalbuminemic states: nephrotic syndrome, advanced liver disease, malnutrition
    - Physical cause: peritonitis, burns, crush injury
    - Peripheral vasodilation: sepsis, antihypertensives
    - bilateral RAS
- Intrinsic
  - acute GN
  - acute interstitial nephritis
  - ATN
- Postrenal
  - must involve obstruction of both kidneys
  - prior abdo/pelvic surgery, cancer, rads
  - periureteral metastatic disease
  - RPF
  - hemorrhage, lymphocele
  - urinary extravasation or fistula formation → may increase Cr due to reabsorption

#### **What is the hallmark of pre-renal azotemia?**

- reversibility w/ treatment of the underlying cause
  - responds to fluid repletion
- lack of structural damage to the kidney

#### **What are the major determinants of the GFR?**

- renal blood flow
- glomerular hydrostatic pressure

## Chapter 8 Questions - ARF+CRF.doc

- glomerular permeability

### What are the characteristics of the urine produced in pre-renal ARF?

- renal hypoperfusion stimulates sympathetic nervous system and RAAS to cause renal vasoconstriction and Na retention, as well as ADH release
- urine produced is low volume, decreased Na concentration, increased urinary Cr excretion, high urine osmolality
- bland urinary sediment

### What is the hepatorenal syndrome (HRS)?

- unique form of pre-renal syndrome: ARF in pst w/ advanced hepatic disease
  - often due to cirrhosis, metastatic ca, EtOH hepatitis
- reduction in renal perfusion relates to relative splanchnic vasodilation
- characterized by oliguria, benign U/A, urinary Na retention, Cr increase

### What is the tx of HRS?

- Surgical: liver transplant → best hope
- Medical: disappointing
  - ACEi: systemic hypotension and decreased GFR
  - ADH analogue: causes renal ischemia
  - PG analogue, midodrine ( $\alpha$  agonist), octreotide
- hemodialysis: for pts awaiting liver tx

### What is the Ddx of RPGN?

- Multisystem disease
  - SLE, Goodpasture's, HSP, necrotizing vasculitis (including WG), cryoglobulinemia, cancer (colon, lung), Behcet's
- Superimposed on primary glomerular disease
  - MPGN, membranous GN, IgA nephropathy
- Infectious
  - post-strep GN, infectious endocarditis, sepsis, hep B, hep C
- Drugs
  - allopurinol, D-penicillamine, hydralazine, rifampin
- Idiopathic
  - Type I: anti GBM disease
  - Type II: immune complex mediated disease
  - Type III: pauci-immune

### What are the U/A findings of AIN?

- sterile pyuria, WBC casts, eosinophiluria

### What can cause AIN?

- Medications
  - NSAIDs
  - pen, cephalosporins
  - rifampin
  - sulfonamides: furosemide, bumetanide, thiazides, TMP/SMX
  - cimetidine
  - allopurinol
  - Cipro, other quinolones?
  - 5-aminosalicylates
  - phenytoin
  - Losec
- Infection
  - Legionella, CMV, EBV, mycoplasma
- sarcoid

### What histologic changes are seen in AIN?

- interstitial edema
- interstitial infiltrate of T cells and monocytes

## **Chapter 8 Questions - ARF+CRF.doc**

### **What is the clinical presentation of AIN?**

- abnormal urine sediment: proteinuria, pyuria, eosinophiluria
- skin rash

### **What is the tx of AIN?**

- remove offending agent
  - renal function usually improves in 3-7d
- steroid or cytotoxic tx may help recovery of renal function and reduce interstitial fibrosis

### **What are the causes of ATN?**

- renal hypoperfusion and renal ischemia
- Exogenous toxin
- Endogenous toxin
  - pigment nephropathy: hemoglobin, myoglobin, methemoglobin
  - intrarenal crystal deposition: urate, Ca, oxalate
  - tumour specific syndromes: tumour lysis syndrome, plasma cell dyscrasias (MM kidney)

### **What exogenous toxins/medications can cause ATN?**

- Antibiotics
  - aminoglycosides, cephalosporins, sulfa, tetracyclines, amphotericin B, polymyxin, bacitracin, pentamidine, vancomycin, acyclovir, foscarnet
- Anesthetics
  - methoxyflurane, enflurane
- Contrast
  - diatrizoate, iohalamate, iopamidol, iopanoate
- Antiulcer meds
  - cimetidine, milk-alkali
- Diuretics
  - mercurials, furosemide
- Chemo
  - cisplatin, carboplatin, ifosfamide, MTX, nitrosourea, plicamycin, cyclosporine, tacrolimus, D-penicillamine, IL-2, IFN
- Analgesics
  - NSAIDs
- HIV Protease inhibitors
  - zidovudine, zalcitabine
- Organic solvents
  - glycols (ethylene glycol), halogenated hydrocarbons, aromatic hydrocarbons (toluene), 5-azacytidine (vaseline, kerosene, turpentine)
- Heavy metals and poisons
  - insecticides (chlorpyrifos), herbicides (paraquat, diquat), rodenticide (elemental P), mushrooms, snake bite, sting, bacterial toxins
- Chemicals
  - aniline, hexol, cresol, chlorates, K bromate
- Recreational drugs
  - heroin, amphetamine
- Misc
  - dextrans, EDTA, rads, silicone, EACA, ACEi

### **What are the characteristics of pigment nephropathy?**

- post-traumatic or atraumatic after intoxications
- hematuria on dipstick, no RBC on micro
- renal hypoperfusion + nephrotoxicity of pigment → ATN
- treatment: forced alkaline diuresis to minimize nephrotoxicity

### **How do protease inhibitors cause renal failure?**

- reversible ARF secondary to crystalluria and intrarenal obstruction
- zidovudine renal stones

## Chapter 8 Questions - ARF+CRF.doc

### Why do ABMT pts get renal failure?

- ATN due to tumour lysis syndrome, bone marrow infusion, sepsis, or antibiotics
- hepatic veno-occlusive disease from endothelial cell injury from chemo or rads: 10-16days
- HUS related to cyclosporine or rads: 4-12mo

What is the natural hx of ATN?

- oliguric phase: begins < 24h after incident, may last 1-3 weeks
  - urine volume: 150-300cc/day
- diuretic phase: progressive increase in urine volume
  - Cr may increase for another 24-48h
  - severe polyuria
  - 25% of deaths from ARF occur now, due to fluid/lyte abnormalities, as well as infection
- recovery phase
  - renal fn returns to baseline

### Why does cellular dysfunction occur during ATN?

- medulla operates at brink of hypoxia during normal function
  - due to countercurrent diffusion of oxygen from descending to ascending vasa recta
  - high metabolic requirements of tubular cells in outer medulla are most sensitive to injury
  - thick ascending limb also metabolically very active: Na-K-ATPase
- depletion of ATP
  - ATP metabolized to AMP
  - AMP → hypoxanthine, adenosine, inosine: all diffuse from cell, resulting in loss of substrate for ATP synthesis
  - accumulation of hypoxanthine → involved in oxygen free radical creation
- ATP depletion causes Na-K-ATPase dysfunction
  - cell swelling results
- Na-Ca-ATPase dysfunction occurs + **reperfusion injury**
  - leads to high intracellular Ca levels → activates calmodulin-dependent protease, converting xanthine dehydrogenase → xanthine oxidase
  - xanthine oxidase converts hypoxanthine → xanthine + superoxide
  - superoxide →  $H_2O_2$  via superoxide dismutase
  - $H_2O_2 \rightarrow 2 OH^\cdot$ 
    - leads to reperfusion injury
- phospholipase activation: leads to damage to lipid bilayer

### What structural changes occur to the tubular cells in ATN?

- loss of cell polarity
  - aberration in cytoskeletal organization of the tubular cells
  - redistribution of Na-K-ATPase to apical membrane
  - causes impaired solute and water transport
- brush border loss
  - brush border debris shed into tubules
  - intratubular cast formation occurs
- impaired cell-cell and cell-matrix adhesion
  - causes detachment of cells and loss of continuity of renal epithelium
- impaired tight junction function
  - permits backleak of glomerular filtrate

### Why is RBF to the medulla reduced in ischemic ATN?

- vasoconstriction
- congestion of the medullary vasculature w/ WBC, RBC, platelets

### How does one diagnose ARF?

- Hx
  - potential nephrotoxic insults
  - evidence of systemic disease
  - level of preexisting renal function
  - RF associated w/ ARF
- Px

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- VS and hemodynamics
- volume status: pt weight, peripheral edema, neck vein distension
- CVP or PA wedge pressure
- Labs
  - urine output
  - urinalysis: sediment, casts → heme granular casts, renal tubular epithelial cells
  - urine lytes
  - urine Cr
  - urine osmolality
- Imaging
  - renal US: hydro may not be present in early obstruction
    - duplex US of renal artery: identify RAS or thrombosis
  - KUB: stones
  - radionuclide renal scan: evaluates for RBF and function
  - radiocontrast studies: limited value during ARF
  - angio: to confirm RAT, RAS, dissection

### What are the RF associated w/ ARF?

- advanced age
- comorbid conditions: CHF, liver failure, renal insufficiency, DM
- contrast exposure
- drugs: aminoglycosides, NSAIDs, ACEi
- atheroembolism
- intraoperative issues: blood loss, hemodynamic stability, GU tract integrity, intraop drug treatment

### How does the urine sediment help in diagnosing ARF?

- bland sediment/normal: prerenal or obstruction
- RBC casts, RBC: AGN or vasculitis
- eosinophils: AIN
- heme granular casts: ATN

### What are the patterns of urinary indices in ARF?

- Prerenal or AGN
  - urine Na < 20
  - urine/plasma Cr > 30 (++ urine Cr)
  - RFI < 1
  - $FE_{Na} < 1\%$
  - urine osmolality > 500
- ATN or obstruction
  - urine Na > 40
  - urine/plasma Cr < 20 (low urine Cr)
  - RFI > 1
  - $FE_{Na} > 1\%$  (3-6%)
  - urine osmolality < 400

### What is the renal failure index?

- $RFI = U_{Na} \times P_{creat} / U_{creat}$

### What are the complications of ARF?

- Fluid overload: htn, edema, acute pulmonary edema
- Electrolyte disturbances: decreased Na/Ca, increased K/Mg/P/Ca/urate, metabolic acidosis
- Uremia: N/V, UGIB
- Neurologic: mental status changes, encephalopathy, coma, seizures, peripheral neuropathy
- Cardiac: pericarditis, uremic CM
- Pulmonary: pleuritis
- Hematologic: bleeding, anemia
- Immunologic: impaired granulocyte and lymphocyte function

### Describe the management of ARF.

## Chapter 8 Questions - ARF+CRF.doc

- General
  - correction of precipitating factors
  - restoration of renal perfusion
  - eliminate nephrotoxic drugs
  - drain obstruction if present
  - control urinary extravasation
- Pharmacologic intervention
  - diuretics: conversion of oliguric to nonoliguric ATN
    - loop diuretics and mannitol: wash out obstructive debris and casts
    - loop diuretics: decrease active NaCl transport in thick ascending limb, limiting energy requirements
  - low-dose renal dopamine (1-3 ug/kg/min)
    - increases oxygen and substrate delivery, inhibits Na-K-ATPase activity, has diuretic effect
    - selective D1 agonists may prevent unwanted D2 s/e (ex: fenoldapam)
  - intrarenal ANP infusion
    - vasodilation of ANP → role uncertain
  - IGF-1, EGF: help tubular regeneration
  - CCB: reverse vascular constriction, increase GFR, improve RBF
- Conservative management
  - Fluid balance: monitor ins/outs + weights, restrict fluids and salt
  - Electrolyte and acid/base balance: prevent hyperK, hypoNa, hyperP, keep bicarb < 15, treat hypoCa if sx
  - Uremia and nutrition: restrict protein, maintain carb intake to minimize ketosis
  - Drugs: review meds, stop Mg-containing meds, give diuretics
- Dialysis

### How does mannitol protect against cellular damage in ATN?

- flushes intratubular casts w/ increased tubular flow rate
- increases RBF and urine flow
- reduces hypoxic cellular swelling
- protects mitochondrial function
- scavenging free radicals

### What are the indications for initiation of dialysis?

- volume overload
- hyperkalemia refractory to medical management
- metabolic acidosis refractory to medical management
- uremic pericarditis
- selected poisonings
- uremic sx

### What potential mechanisms from HD may be detrimental on the course of ARF from ATN?

- fall in urine volume
- dialysis-induced hypotension
  - autoregulation impaired in ATN, so pts sensitive to hypoperfusion
- complement activation
  - blood interaction w/ membranes

### What is the prognosis of ATN?

- depends on underlying primary disease causing ARF
  - mortality rate for pts w/ ATN is 50%
- if pts survive, 50% have complete recovery of renal function, 40% have partial recovery
- **"you either die or you get better"**

### How can one prevent ATN?

- precontrast IV hydration
  - no effect w/ addition of loop diuretic or mannitol
- acetylcysteine (600mg PO BID on day before and on day of contrast): antioxidant
- nonionic contrast

### How does reduction in renal mass predispose to CRF?

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- initiates cycle of progressive glomerular injury in the renal remnant
  - injury associated w/ hyperfiltration, glomerular hypertrophy and systemic hypertension
- age at time of loss of renal mass influences kidney's response
  - volume of glomeruli in congenital solitary kidney is 5-6X in normal kidney

### What remodelling events occur in the kidney after a decrease in functioning renal mass?

- Neurogenic response
  - increase in ANGII and NO levels
  - activation of sympathetic nervous system
- Structural alterations
  - glomerular hyperplasia and hypertrophy
  - increased ECM production
  - glomerular BM modification
  - podocyte denudation
- Altered gene expression
  - changes in MMP expression or activity
  - ACE polymorphisms
  - ECM proliferation
- Mechanisms of progression
  - glomerulosclerosis
    - due to loss of renal mass, high protein/salt diet, GH, IGF-1, androgen, steroids, angiotensin, endothelin
    - prevented by ACEi
  - interstitial fibrosis: from chronic oxygen deprivation

### What are the causes of CRF?

- Systemic diseases
  - DM, htn: 72% of cases
    - once proteinuria occurs and renal function declines, 50% pts reach ESRD in 7-10yrs
  - GN
  - SLE, HSP, systemic sclerosis
  - dysproteinemias, amyloid
  - thrombotic microangiopathies
  - vasculitis: crescentic GN, WG, Churg-Strauss, Goodpasture's
- Primary renal disease
  - GN, minimal change disease, FSGS, membranous, IgA nephropathy
- Tubulointerstitial disease
  - hematopoietic: sickle cell, lymphoproliferative, dysproteinemia, neoplastic
  - urologic: ureteral obstruction, VUR, prune-belly, BPH
  - vascular: rads, htn, atheroemboli
  - metabolic: cystinosis, oxalosis, uric acid nephropathy, hypercalcemia
  - immunologic: renal allograft rejection, Sjogren's
  - toxic: analgesic, NSAID, chemo
  - immunosuppression: FK506, cyclosporine
  - heavy metals: Pb, Li
- Hereditary disease
  - sickle-cell
  - cystic disease: ADPKD, MCD
  - Alport's syndrome

### What primary parenchymal renal disease have the greatest propensity to progress?

- FSGS, RPGN, chronic GN, and MPGN

### What factors can lead to acute worsening of renal function in CRF?

- Nephrotoxic: contrast, aminoglycosides, NSAIDs, COX-2 inhibitors, chemo, cyclosporine, anesthetics
- Autoregulatory dysfunction: ACEi, AT2-R blocker
- Anatomic: ADPKD and ACEi, obstruction, RAS, RVT, stones
- Hemodynamic: CHF, hypotension, MI, valvular disease
- Parenchymal injury: new GN
- Interstitial: hyperCa, hyperuricemia, atheroemboli



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- Drug-induced: pen, cephalosporins, sulfa, rifampin
- Diuretics: thiazides, furosemide
- Misc: phenytoin, allopurinol, cimetidine

### What factors increase the risk of progression from CRF to ESRD?

- htn
  - pts w/ better BP control have slower rates of kidney function deterioration
  - **ACEi** may control BP and reduce proteinuria
  - **HMG-CoA reductase inhibitors** reduce production of molecules involved in fibrogenesis
- microalbuminuria
  - ramipril reduces progression from microalbuminuria to nephropathy
- proteinuria
  - CCB slow proteinuria and renal scarring
- poor DM control
- smoking
- high dietary protein
  - protein restriction can slow sx
- hyperlipidemia

### What are the most important markers of poor outcome in ESRD?

- advanced age
- CAD
- DM
- poor nutrition (hypoalbuminemia)

### How do the outcomes of renal replacement therapy (RRT) change w/ race and gender?

- black pts: poorer outcomes → anemia, access problems, htn, poor HD, noncompliance, decreased transplantation
- females: poorer outcomes → more frequent hospitalizations, anemia, access problems, malnutrition, poor QOL, dec transplant

### Which pts will not benefit from RRT?

- profound irreversible neurologic impairment
- pts w/ terminal illness
- pts w/ medical condition that prevents HD
- pts that refuse HD

### How are pts outcomes on PD vs. HD?

- increase in survival when pts switched to PD from HD
- RRF preserved longer on PD
- BP better controlled and ventricular arrhythmias observed less often on PD
- wt gain and inadequate dialysis more common w/ PD

### What are the reasons for switching b/w HD and PD?

- HD → PD
  - access problems
  - hemodynamic instability
- PD → HD
  - PD peritonitis
  - inadequate dialysis
  - catheter malfunction

### What are the criteria for initiation of RRT in hospitalized pts?

- oliguria < 200cc/12h
- anuria < 50cc/12h
- hyperK > 6.5
- severe acidemia: pH < 7.1
- azotemia: BUN > 30
- significant organ edema (lung)
- uremic encephalopathy

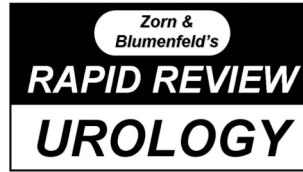
## Chapter 8 Questions - ARF+CRF.doc

- uremic pericarditis
- uremic neuropathy
- severe dysnatremia: Na > 160 or < 115
- drug OD w/ dialysable toxin

### What are the components of an optimal disease management program for pts w/ ESRD?

- Interventions that delay progression
  - ACEi
  - BP control
  - DM control: target Hb<sub>A1c</sub> of < 7%, fasting BG 8-12, night BG 10-14
  - hyperlipidemia control
  - protein restriction
- Prevention of uremic complications
  - treat malnutrition, osteodystrophy, anemia, hypervolemia, edema, acidosis
    - EPO if anemia
- Modification of morbidity
  - DM control
  - treat PVD
  - treat CAD
  - treat pulmonary disease
- Preparation for RRT
  - renal disease education
  - modality selection
  - timely access placement
  - timely dialysis initiation





## Chapter 9

### • Basic Principles of Immunology in Urology •

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#### **What cells can perform phagocytosis?**

- neutrophils, macrophages, reticuloendothelial cells (Kupffer cells in liver, bronchial alveolar macrophages)
  - enhanced by C3b and I that bind microbes: act as opsonins

#### **What is complement?**

- collection of 20 soluble proteins: can directly lyse invading bacteria and viruses
  - complement activation results in cascade phenomena
  - C3a and C5a are powerful anaphylotoxins, chemoattractants
- Classical pathway
  - Ag-Ab complex fixes C1q to cell surface
  - C1q + C2 + C4 → C4b2a + C3 → C4b2a3b + C5 convertase → C5b → C6-9 activated: MAC (membrane attack complex)
- Alternative pathway
  - bacterial endotoxin and microbial polysaccharides + properdin activate C3 directly
  - non-Ab dependent
  - C3bBbP + C3 convertase → C3bBbP + C5 convertase → C5b → C6-9

#### **What are the primary and secondary lymphoid tissues?**

- Primary
  - bone marrow: responsible for B cell differentiation
  - thymus: responsible for T cell differentiation
- Secondary
  - spleen, LN, unencapsulated tissue in GI, respiratory, GU tracts

#### **What are the different types of lymphocytes in the body?**

- B lymphocytes
  - responsible for Ig production
  - single B cell produces only one Ab specific for one antigenic determinant (epitope)
- T lymphocytes
  - originate in bone marrow, migrate to thymus
  - responsible for cell-mediated immunity
  - all have CD3 T cell marker
  - during maturation, CD4<sup>+</sup>CD8<sup>-</sup> T cells develop into CD4<sup>+</sup>CD8<sup>+</sup> cells, then become either CD4<sup>+</sup>CD8<sup>+</sup> (T<sub>H</sub> cells) or CD4<sup>+</sup>CD8<sup>-</sup> (T<sub>K</sub> cells)
- NK cells
  - natural killer cells are large granular lymphocytes that can destroy nucleated cells and virus infected cells
  - do not require prior contact w/ Ag, and are not MHC restricted
  - release cytotoxic factors
- PMNs
  - either neutrophils, eosinophils, or basophils
  - binding of Ag to surface IgE causes them to degranulate, resulting in type I hypersensitivity
  - if basophils are fixed to tissue, are called mast cells
- monocytes and macrophages
  - liver: Kupffer cells
  - lung: alveolar macrophages
  - connective tissue: histiocytes
  - brain: microglia
  - kidney: glomerular mesangial cells
- Ag presenting cells (APCs)

## Chapter 9 Questions - Immunology.doc

- includes macrophages, monocytes, B cells, Langerhans cells, dendritic reticular cells, vascular endothelium
- Vascular endothelial cells
  - if activated by inflammation or antigen, they express adhesion molecules, selectins, chemotactic factors, and MHC

### What is the MHC?

- major histocompatibility complex: region of genes on chromosome 6
- code for cell surface markers
  - dimers, w/ alpha and beta chain → form unique peptide-binding cleft
- called human leukocyte antigens in humans (HLA)
- 2 major classes:
  - HLA class I: on all nucleated cells (HLA-A, -B, -C)
  - HLA class II: primarily found on B cells, monocytes, macrophages, and APCs (HLA-DP, -DR, -DQ)
- each person has 2 class I and 1 class II from each parent: 6 HLAs in each individual tissue type

### What is the TCR?

- cell surface structure responsible for the initial steps in T cell activation on encounter w/ Ag
- $\alpha$  and  $\beta$  chains, and CD3 chains: CD3 present on all T cells
  - 2 different types of TCR: TCR1 and TCR2

### Describe how T cells become activated.

- Presentation of Ag
  - deposition of antigenic material induces a local inflammatory response
    - initiated by TNF- $\alpha$  and IL-1 in response to tissue trauma
  - interstitial dendritic cells are activated by TNF- $\alpha$  to become phagocytic cells and ingest foreign material and tissue debris
    - Ag uptake by cell, proteolysis, and repackaging
  - T cells w/ CD8 ( $T_K$ ) require APCs to present Ag in context of MHC class I
  - T cells w/ CD4 ( $T_H$ ) require APCs to present Ag w/ MHC class II
  - Ag must be processed in small pieces, processed in MHC
- Recognition of Ag
  - TCR-CD3 complex must see Ag in MHC on APC
  - "signal 1": stabilized by appropriate T cell coreceptor (CD4 or CD8)
  - "signal 2": costimulation by proteins on APC: B7-1 and B7-2 engage T cell surface glycoprotein CD28, or CD40 stimulates CD40L
- Clonal expansion
  - TCR engagement of specific ligand w/ costimulation induces expression of IL-2
    - stimulates clonal proliferation of CD4 cells in autocrine manner
  - IL-15 important in CD8 cell production
- Cytokine production
  - CD4  $T_H$  cells develop into cells producing type 1 cytokines ( $T_H1$  cells) or cells producing type 2 cytokines ( $T_H2$  cells)
    - ◆ Type 1 cytokines: IFN- $\gamma$  and TNF- $\beta$
    - ◆ Type 2 cytokines: IL-4, IL-5, IL-6, IL-9: critical components of immune response
- Cytolysis of target cells
  - 2 mechanisms utilized by  $T_K$  cells (CD8) to mediate cytolysis
    - intracellular granules of perforin and serine esterases: release these granules
    - expression of Fas ligand (FasL): induces apoptosis

### How do cells recognize alloantigen?

- direct recognition
  - recipient T cells engage MHC-peptide molecules expressed on allografts
  - donor MHC molecule w/ peptide derived from donor or recipient protein, or no protein
  - responsible for acute rejection of allografts
- indirect recognition
  - T cells recognize processed alloantigens presented by recipient APCs in association w/ self-MHC class II molecules
  - recipient MHC molecule w/ peptide derived from donor proteins
  - requires uptake and processing of donor MHC molecules by recipient APC
  - recipient APCs migrate to the graft and take up soluble MHC molecules for processing
  - more closely linked to chronic rejection

## Chapter 9 Questions - Immunology.doc

### How are B cells activated?

- require help of CD4 T cells to differentiate into plasma cells
- B cell Ig R react w/ protein Ag and Ag are endocytosed, processed, and transported to the cell surface in the context of MHC II
- T<sub>H</sub> cell TCR is engaged and stabilized by CD4, leading to T cell activation and secretion of IL-2
- 2<sup>nd</sup> costimulation by B cell surface marker CD40 and its ligand CD40L on the T<sub>H</sub> cell
- secrete IgM after primary exposure
  - re-exposure results in production of IgG or IgA antibodies

### Describe the signal transduction pathway induced by the TCR.

- binding of Ag to TCR causes activation of Lck, which results in phosphorylation of TCR $\zeta$  and recruitment and activation of another tyrosine kinase (ZAP-70)
- ZAP-70 phosphorylates LAT and SLP-76
- LAP recruits PLC to cleave PIP2 into IP3 and DAG
- IP3 increases intracellular calcium, which activates the phosphatase calcineurin
  - activated calcineurin dephosphorylates NFAT, which translocates to the nucleus
- DAG release leads to the activation of PKC
- phosphorylated LAT results in activation of Ras
  - activated Ras recruits Raf-1 to the membrane, where it is activated
  - Raf-1 activates the kinase Mek, which activates other kinases in the pathway

### Describe the mechanisms that allow for self-tolerance by the immune system.

- Central tolerance
  - deletion of self-reactive T and B cells during maturation
  - maturation of T cells in thymus: +ve selection
    - T cell precursors go to thymus, express CD3, CD4 and CD8
    - maturation completed as cells react w/ MHC I or II cells in thymus, and become either CD4 or CD8 cells
    - T cells expressing receptors that do not engage MHC undergo apoptosis: absence of survival signals
  - -ve selection
    - T cells expressing receptors that have very high reactivity to complexes of self-peptides and MHC receive signals to undergo apoptosis
- Peripheral tolerance
  - administration of large Ag doses stimulate rapid proliferation of reactive T cells
    - quickly followed by apoptosis of reactive cells
    - deletion due to "clonal exhaustion"
- Clonal anergy
  - induced by TCR engagement of peptide-MHC complexes in the absence of costimulatory signals
  - T cells are unable to clonally expand

### How are leukocytes localized to sites of vascular inflammation?

- begins w/ regulated expression of adhesion molecules and their ligands on the WBC and endothelial cells
- engagement of selectins tethers the cells and slows their movement
- binding of integrins to Ig receptors mediates the arrest of the T cells on the vascular endothelium
- diapedesis: cell traverses the endothelial barrier into peripheral tissue
  - platelet/endothelial cell adhesion molecule-1 (PECAM-1) concentrated at the cell junctions in the vessel

### What are the functions of chemokines?

- recruitment of WBC
- trigger arrest of monocytes and T lymphocytes
- stimulate increased integrin expression and cell adhesion
- stimulate the release of granules by neutrophils and granulocytes
- amplify CD8 and NK cell mediated cytotoxicity

### Why are tumour cells poor stimulators of T cells?

- lack of expression of MHC II molecules
- variability of expression of MHC I molecules

### What are the mechanisms by which tumour cells can induce immune dysfunction in T cells and dendritic cells?

- defective antigen processing and presentation
  - loss of MHC I and II expression by tumours

### Chapter 9 Questions - Immunology.doc

- decreased expression of transporter proteins
- decreased levels of LMP
- secretion of immunosuppressive products
  - secretion of IL-10, TGF- $\beta$  (inhibits IL-2), PGE<sub>2</sub>

### What is the difference b/w *antigenic drift* and *antigenic shift*?

- antigenic drift = minor changes in surface Ag due to pt mutations in viral genome
- antigenic shift = major changes arising from exchanges of large portions of the viral genome w/ other viruses

### What is the T $\frac{1}{2}$ of Ig?

- 1-2 weeks



## Chapter 10

### • Renal Transplantation •

---

#### **What are the advantages of living related donor transplants?**

- better graft survivals
- less recipient morbidity
- limitation of waiting time
- alleviation of insufficient supply of cadaveric kidneys

#### **What characteristics make a patient suitable or unsuitable for PD?**

- Suitable
  - desire for self-care
  - long distance from HD unit
  - difficulties w/ HD
  - serious cardiac disease
  - DM
  - small stature
- Unsuitable
  - obesity
  - hernias
  - poor hygiene
  - obliterated peritoneal space

#### **What are the risks of mortality of various renal replacement therapies?**

- all dialysis pts: 1.0 risk ratio (reference)
- dialysis pts on waiting list for transplant: 0.48
- cadaver kidney transplant recipients: 0.32
- living related: 0.21

#### **How does one screen a potential transplant recipient?**

- Hx/Px
  - Preliminary screen (SOCM – substance, obesity, compliance, medical)
    - prior substance abuse: drug screen
    - morbid obesity > 100lbs / 50% over desirable weight, BMI > 35: weight loss
    - compliance problems: contract
    - hx CAD, DM: medical evaluation
      - ◆ if any of these fail, pt unacceptable for transplant
  - PMHx: assess risk of disease recurrence in kidney graft: HUS, primary oxalosis, FSGS
  - Meds
  - Immunizations
  - FOB
  - Pap smear
- Labs
  - CBC, lytes, BUN, Cr, INR, PTT, LFT
  - UA, urine C&S
  - serologies: CMV, HSV, EBV, HIV, hep B/C, TB skin test
  - **histocompatibility testing**
  - PSA
  - CXR
  - ECG
  - abdo US
  - mammogram: if F > 40
  - eye exam: if >50 or DM
- **RULE OUT:** MOpNIT (malig, op mortality, tech, infection, noncompliance)



## Chapter 10 Questions - Transplant.doc

- R/O active infection
  - dental sepsis (dental exam), HD access sites, pulm infx, TB skin tests
  - cholecystectomy if cholecystitis
  - segmental colectomy if diverticulitis
  - diabetic foot ulcers must be healed
  - screen for CMV, HSV, EBV, HIV, hep B/C
  - give immunizations: hep A/B, pneumococcus, DTP, polio, varicella, MMR
- R/O active malignancy
  - wait 2-5 years from time of last cancer treatment for invasive malignancy
- R/O high chance of operative mortality
  - CAD: most common cause of death post-tx
  - treat CAD, PUD, COPD
  - **must quit smoking**
- R/O noncompliance
  - drug abuse: free for > 6mo
  - financial counseling
  - psychosocial consult
- R/O unsuitable conditions for technical success
  - vascular disease: Doppler studies, plan for revascularization surgery if needed
  - hypercoagulable state: factor V Leiden, protein C, protein S, antithrombin III, homocysteine level, antiphospholipid Ab
  - urologic disease: voiding dysfunction, hematuria, bacteriuria, stones, hydro, VUR, PCKD, pyelo

### Which diseases recur in a transplant kidney?

- FSGS
  - increased risk if: <15 yrs, RPGN, mesangial proliferation on bx, hx failed transplant
    - risk failure 80% if previous failed transplant from recurrent FSGS
- primary oxalosis
  - transplant liver and kidney to cure metabolic defect
- HUS
- DM
- IgA nephropathy
- cystinosis
- Fabry's disease (fat man's disease)
  - lipid storage disorder caused by the deficiency of ceramidetrihexosidase (also called alpha-galactosidase A)
  - enzyme involved in the biodegradation of fats: insufficient breakdown of lipids, which then build up in the body
- renal amyloid

### What are the indications for a pre-transplant cholecystectomy?

- symptomatic cholecystitis
- multiple small stones
- cholelithiasis w/ GB wall thickening

### What are the recommended cancer-free waiting times from last cancer treatment before renal transplant?

- 0 years: small/incidental RCC, noninvasive bladder TCC, BCC
- 2 years: large/invasive RCC, Wilms', invasive bladder TCC, testis ca, prostate ca, thyroid ca, lymphoma, SCC
- 2-5 years: breast ca, colon ca, melanoma

### What is the risk of giving an EBV+ kidney to an EBV- recipient?

- risk of PTLD (post-transplant lymphoproliferative disorder)
  - commonest new malignancy in pediatric organ transplant recipients

### What is the treatment of chronic active hepatitis B/C during transplantation?

- evolving: combination of IFN-alpha and ribavirin

### What are the indications for Doppler flow studies in renal transplant candidates?

- cerebrovascular sx or bruits
- lower extremity claudication or bruits
- extensive aortoiliac calcification or bruits
- prior bilateral renal transplant

## **Chapter 10 Questions - Transplant.doc**

- prior abdominal vascular surgery
- prior rads
- prior pelvic venous thrombosis

### **What pts are at risk of graft thrombosis?**

- previous vascular access graft thrombosis
- previous DVT
- antiphospholipid Ab
- previous large vein renal transplant thrombosis
- nephrotic syndrome: loss of natural anticoagulants (antithrombin III, protein C, protein S)
- hyperhomocysteinemia

### **What are the indications for additional urologic studies in renal transplant candidates?**

- to determine the suitability of the bladder for reconstruction, and to determine the need for pre-tx nephrectomy
  - voiding dysfunction, hx pyelo/VUR, poor US: VCUG + UDS
  - suspected lower urinary tract ca: cysto
  - planned orthotopic renal transplant, poor US: retrograde pyelogram
  - ADPKD, poor US for stone or mass: CT abdo
  - hx cyclophosphamide, significant LUTS: cytology
  - hematuria, suspected bladder fibrosis or TCC: cysto + bladder bx
  - conduit/reservoir: loopogram or pouchogram
  - single organism bacteriuria
  - stones
  - hydro
  - significant PVR

### **What are the indications for pre-transplant nephrectomy?**

**(SHMAPPP – stones, hydro, mass, Ab, polycystic, pyelo, proteinuria)**

- renal calculi not cleared by minimally invasive techniques or ESWL
- solid renal mass +/- ARCD
- PCKD: symptomatic, ++ large (below iliac crest), infected, solid tumours
- persistent anti-GBM Ab levels
- significant proteinuria not controlled w/ medical nephrectomy or angioablation
- recurrent pyelo
- severe hydro (grade 4-5)

### **What are the basic criteria for a renal donor?**

- absence of renal disease
- absence of active infection
- absence of transmissible malignancy

### **Which kidney is normally taken for transplant?**

- usually take L kidney for longer renal vein
- better kidney left w/ donor
- use R kidney in women that may become pregnant
  - hydro and pyelo occur mostly in that kidney

### **What are the contraindications to donor nephrectomy?**

- significant transmissible disease/infection/ca
- significant renal disease
- significant mental dysfunction
- high risk of perioperative mortality or morbidity
- ABO incompatibility
- +ve cross match b/w donor lymphocytes and recipient serum
- significant abnormality seen on donor workup: cardiac, neoplastic, endocrine, infectious
- unacceptable renal anatomy: multiple vessels, ureters

### **What is the algorithm for evaluation of a potential renal donor?**

- Preliminary
  - Hx: PMHx, Meds, BP

## Chapter 10 Questions - Transplant.doc

- Px
- Labs: CBC, lytes, BUN, Cr, UA, ABO blood type, donor-recipient crossmatch
- Contraindications?: ca, poor renal fn, infection, crazy, high operative risk, ABO, anatomy
- Complete testing
  - Hx, Px
  - Ix
    - CBC, lytes, BUN, Cr, LFT, Ca profile, coags, UA, urine C&S
    - infectious serologies
    - ECG, CXR, cardiac evaluation
    - pap smear, mammogram
    - pregnancy test → R kidney usually taken in women that may become pregnant: more often has hydro/pyelo
    - PSA
    - random blood sugar, glucose tolerance test
    - renal US
    - CT abdo: assess vessels, excludes stones, demonstrate renal anatomy, define collecting system
    - FOB
  - Consults
    - social services
- Repeat: imaging, b/w, crossmatch

### What are the criteria for an ideal cadaveric kidney donor?

- normal renal function
- no htn requiring tx
- no DM
- no malignancy other than superficial treated skin cancer or primary brain tumour
- no generalized bacterial, viral infections
  - blood cultured if in hospital for > 72 hrs
- acceptable UA
- age 6-45
- -ve serologies for syphilis, hep, HIV, HTLV

### What are the goals of resuscitation for a brain-dead donor?

- sBP > 90 mmHg
  - if cannot maintain BP and CVP > 15 cm water, dopamine or dobutamine < 10 ug/kg/min
  - temporary pacer if bradycardia despite atropine, dopamine, dobutamine
- u/o > 0.5 cc/kg/hr
  - if cannot maintain u/o, Lasix 1mg/kg +/- mannitol 0.5-1 mg/kg IV
  - if ++ u/o from DI, IV vasopressin
- check lytes q2h
- keep head warm, IV fluids warm
- tissue typing and X-match

### What is the cause of warm ischemic injury in donor nephrectomy?

- failure of oxidative phosphorylation and cell death due to ATP depletion
- Na-K-ATPase is impaired, NaCl and water passively diffuse into cells → cellular swelling and death
  - "no-reflow" phenomenon

### How are kidneys best stored after donor nephrectomy?

- cellular energy requirements reduced by cooling
  - surface cooling
  - hypothermic pulsatile perfusion: superior to simple cold storage in kidneys w/ significant warm ischemic time
  - flush w/ hyperosmolar ice solution to prevent cellular swelling

### What is UW solution?

- balanced electrolyte solution
  - impermeant solutes: lactobionate, raffinose, hydroxyethyl starch
    - makes solution slightly hyperosmolar to prevent cell swelling
  - phosphate: for H<sup>+</sup> buffering
  - adenosine: for ATP synthesis
  - glutathione: free-radical scavenger

## Chapter 10 Questions - Transplant.doc

- allopurinol: inhibits xanthine oxidase and generation of free radicals
- Mg, dexamethasone: membrane-stabilizing agents

### What are the indications for ureteroureterostomy and pyeloureterostomy in renal transplantation?

- short or ischemic allograft ureters
- limited bladder capacity
- surgeons preference

### Describe the technique of renal transplantation.

- Pre-op
  - prophylactic antibiotic
  - immunosuppression started just before or during surgery
  - GA + monitors
  - Foley catheter attached to irrigant solution +/- antibiotics
- Procedure
  - kidney graft placed extraperitoneally in contralateral iliac fossa via Gibson incision
  - maintain CVP at 5-15 cm H<sub>2</sub>O
  - heparin 30u/kg given IV prior to temporary vascular occlusion
  - mannitol given during anastomosis: free-radical scavenger and osmotic diuretic
  - retract cord, divide round ligament
  - renal artery anastomosed to internal iliac artery
    - atherosclerosis: endarterectomy
    - orthotopic renal transplantation if pelvic vessels unsuitable: splenic/renal artery + IVC/renal vein
  - renal vein anastomosis
    - usually end-side to external iliac
    - if renal vein short, helpful to completely mobilize external iliac vein by dividing gluteal and internal iliac branches
    - if child is recipient, shorten renal vein to prevent redundancy
  - lasix just before release of vascular clamps
  - verapamil into arterial circulation: protects kidney from reperfusion injury
  - ureteroneocystotomy
  - ureteral stent: reduces ureteral complications
  - conduit: do not interfere w/ stoma + appliance
  - double transplant: into each fossa or into same fossa
    - 1<sup>st</sup> transplant to IVC and common iliac, 2<sup>nd</sup> transplant to external iliac vein and external or internal iliac artery
  - closed suction drain in subQ tissues in obese pt
- Post-op
  - D5 ½ NS to replace insensible losses
  - ½ NS to replace previous hour's u/o
  - lytes q4-8h
  - U/S
  - urine C&S prior to Foley removal, give antibiotic

### In a pt undergoing repeat transplant w/ previous internal iliac anast, why should one not use the contralateral internal iliac?

- to preserve blood to corpora and reduce the risk of iatrogenic impotence

### What is the only exception to mandatory ABO compatibility requirements in transplant recipients?

- may transplant ABO blood group A<sub>2</sub> kidneys into blood group O and B recipients
  - have low anti-A<sub>2</sub> Ab levels

### What are the 6 HLA antigens?

- Class I: HLA-A, HLA-B, HLA-C
- Class II: HLA-DR, HLA-DQ, HLA-DP

### What are the various immunosuppressants that can be used post renal transplantation?

- Reduction of gene synthesis
  - glucocorticoids
- Purine synthesis inhibition
  - azathioprine

## Chapter 10 Questions - Transplant.doc

- MMF
- Cell cycle progression inhibition
  - sirolimus (rapamycin)
- Calcineurin and IL-2 production inhibition
  - tacrolimus
  - cyclosporin
- T lymphocyte depletion
  - muromonab CD4 (OKT3)
  - rabbit antithymocyte globulin (Thymoglobulin)
  - equine ATS (Atgam)
- IL-2 receptor blockers
  - basiliximab (Simulect)
  - daclizumab (Zenapax)

### What are the sites of action of each of the following immunosuppressants:

- OKT3: alloantigen → TCR
- CSA, tacrolimus: TCR → activated calcineurin
  - both are metabolized by cytochrome P450
  - use diltiazem or ketoconazole to reduce dosing and cost while keeping levels up
- steroid: dephosphorylation of NFAT → IL-2 gene promotion
- IL-2 R blocker: IL-2 → IL-2 R
- sirolimus: IL-2 → progression into cell cycle
- azathioprine, MMF: progression into cell cycle → cell proliferation

### How can one classify rejection?

- Hyperacute rejection
  - immediately after revascularization
  - mediated by preformed circulating cytotoxic antibodies
    - develop after pregnancy, blood transfusions, earlier failed tx
    - rare to have if previous cross-match –ve
- Accelerated rejection
  - mediated by humoral and cellular components of the immune response
  - occurs within days to weeks
- Acute rejection
  - can occur anytime after transplant
  - Sx: pain over enlarged graft, htn, decreased u/o, fluid retention, increased Cr, renal scan indicated decreased RBF, GFR
  - must r/o pyelo
  - Tx: high dose pulse steroids
    - steroid-resistant: antilymphocyte Ab
- Chronic rejection
  - gradual decline in renal function
  - associated w/ interstitial fibrosis, vascular changes, and minimal monocyte infiltration

### What are the complications of renal transplantation?

- Rejection
  - hyperacute
  - acute
  - subacute
  - chronic
- Vascular
  - kinking of renal artery/vein
  - renal graft thrombosis
  - renal artery thrombosis
  - renal vein thrombosis
  - renal artery stenosis: due to atheroma, bad technique, clamp trauma, immunologic mechanisms
    - treat w/ PTA +/- stent
  - AV fistula
  - bleeding
  - lymphocele

## Chapter 10 Questions - Transplant.doc

- renal allograft rupture
  - usually due to acute rejection or renal vein thrombosis
  - requires repair w/ bolstered mattress sutures, topical thrombotic agents, synthetic glue and mesh wrap
- Urologic
  - ED
  - urinary extravasation
  - hematuria
    - treat w/ CBI, endoscopy w/ declotting, fulgurization
  - obstruction
  - UTI
    - *Candida* cystitis: bladder irrigation w/ amphotericin B +/- PO ketoconazole or fluconazole
    - CSA/tacrolimus must be dose reduced if on ketoconazole
    - hemorrhagic cystitis: due to adenovirus, usually self-limited, treat w/ PO forced fluids
- GI
  - bowel obstruction
  - gastritis
  - pancreatitis
  - appendicitis
  - PUD
  - colonic perforation
- Malignancy
  - skin cancer
  - NHL
  - Kaposi's
- Endocrine
  - new onset DM 2° steroids, calcineurin inhibitors

### What are the different causes of early graft dysfunction?

- Infection: F/C, normal or decrease BP, +/- lung findings, +/- transplant tenderness
  - get CXR, U/A, sputum/blood/urine/drainage smear/culture, U/S abdomen
- Rejection: F/C, normal or increase BP, normal or increase CVP, transplant tenderness
  - U/S graft, biopsy
- Obstruction: normal VS, +/- renal transplant tenderness
  - irrigate Foley, U/S graft
- Calcineurin inhibitor toxicity: no fever, normal or increased BP, normal CVP, +/- tremor
  - get CSA/tacrolimus level
- Hyperglycemia: afebrile, decreased BP, decreased CVP
  - BG level
- Dehydration: afebrile, decreased BP, decreased CVP
  - IV fluid bolus

### How can one differentiate b/w cyclosporin/tacrolimus (calcineurin inhibitor) toxicity and acute rejection?

- Cyclosporin toxicity
  - no fever
  - normal U/O
  - no graft tenderness
  - normal graft size
  - slow increase in Cr
  - high CSA/tacrolimus serum level
  - normal graft biopsy
- Acute rejection
  - fever
  - decreased U/O
  - graft tenderness present
  - increased graft size
  - rapid rise in Cr
  - normal or low CSA/tacrolimus level
  - biopsy: cellular infiltration, vasculitis, tubulitis

### What are the indications for allograft nephrectomy?

## **Chapter 10 Questions - Transplant.doc**

- remove a symptomatic irreversibly rejected transplant
- chronically rejected kidney: to withdraw immunosuppression and prevent development of anti-HLA Ab the could delay or prevent subsequent transplantation

### **Describe the technique of transplant nephrectomy.**

- through original incision
- dense fibrous capsule surrounds kidney
- occlude vascular pedicle w/ large vascular clamp
- transect pedicle distal to clamp
- suture ligate renal veins and arteries
- d/c immunosuppression
  - CSA/tacrolimus stopped immediately
  - azathioprine/MMF/sirolimus continued for 4-6 weeks for residual allograft material
  - steroids tapered: 1 week of taper for every month of immunosuppression, to max of 6 weeks

### **What are the causes of hematuria post-renal transplantation?**

- usually catheter trauma or GU tract reconstruction
- medical renal disease in kidney graft
- infection
- stone
- malignancy

### **What is the management of fluid collections after renal transplantation?**

- US guided aspiration
  - large
  - associated w/ hydro
  - pain, fever, or declining renal function
- antibiotics if purulent
  - continue CSA/tacrolimus
  - azathioprine/MMF/sirolimus d/c/d
  - steroids reduced to 15mg/day
- urinary extravasation
  - open repair
  - bladder drainage
  - perc NT
- marsupialization of lymphoceles

### **What are the causes of urinary tract obstruction post renal transplantation?**

- Immediate post-op
  - technical error
  - edema
  - blood clot
  - unsuspected donor calculus
  - perigraft fluid collection
- Later
  - periureteral fibrosis
  - stone
  - cancer
  - fungus ball
  - lymphocele
  - chronic ischemia of distal ureter w/ stricture

### **What are the causes of stones after renal transplant?**

- persistent hyperparathyroidism
- recurrent UTI
- foreign body: suture or staple
- decrease fluid intake
- distal RTA
- stone unknowingly transplanted w/ kidney

## Chapter 10 Questions - Transplant.doc

### What is the algorithm for evaluation of renal transplant hydronephrosis?

- Lasix renal scan
  - $T \frac{1}{2} < 10\text{min}$ : no obstruction
  - $T \frac{1}{2} 10\text{-}20\text{min}$ : equivocal
    - perc nephrostomy + nephrostogram
    - Whitaker test
  - $T \frac{1}{2} > 20\text{min}$ : obstruction → repair

### How does TMP/SMX change Cr levels?

- TMP interferes w/ tubular secretion of Cr → can increase Cr levels

### What are the causes of ED after renal transplantation?

- Central
  - antihypertensives: clonidine, methyldopa, propranolol
  - peptides or amino acids: prednisone → decreased CRH
  - decreased T: cimetidine, cyclosporine → increase PRL
  - anxiety → increase NE
- Autonomic/peripheral nerve injury: DM, uremia
- Blood supply problem
  - internal iliac: RAS
  - accelerated atherosclerosis
  - antihypertensives
  - diuretics
- Cavernosal smooth muscle
  - DM, increased cholesterol, cyclosporine
- Tunica albuginea
  - Propranolol: Peyronie's

### How does one evaluate men w/ ED after renal transplantation?

- Hx/Px
  - Meds
  - Transplant OR
  - GU exam
- Ix
  - NPT
  - test injection
  - CBC, lytes, serum T

### What are the treatments of ED after renal transplantation?

- Psychotherapy
  - stop EtOH, smoking
  - alternate sexual techniques
- Change to current meds
  - d/c cimetidine
  - d/c beta blockers
  - d/c steroids
- Medical therapy
  - T replacement
  - thyroid replacement
  - PDE5 inhibitors
- Vacuum devices
- ICI
- Vascular reconstruction
- Penile prosthesis: malleable, inflatable (w/o prevesical reservoir) → may interfere w/ GU tract reconstruction

### What is required for a penile prosthetic post renal transplant?

- stable graft function w/o rejection for 6mo
- low doses of maintenance immunosuppression
- low probability of device malfunction
- no intra-abdominal components
- minimal tissue dissection



## **Chapter 10 Questions - Transplant.doc**

- no skin infection or UTI
- prophylactic antibiotic for 2 weeks

### **How does pregnancy affect renal transplantation?**

- male: impregnation should be delayed for 1 year post transplant
- female: need good general health for 2yrs post transplant, minimal proteinuria, no htn, no rejection, no UTI, normal Cr, low dose of immunosuppression

### **What immunosuppressants can and cannot be used in pregnancy?**

- No fetal risk in animal studies, no controlled studies (B)
  - steroids, basiliximab
- Fetal risk cannot be ruled out (C)
  - MMF, sirolimus, CSA, tacrolimus, OKT3, RATS, daclizumab
- Evidence of fetal risk (D)
  - azathioprine

### **What are the most common cancers in renal transplant recipients?**

- skin cancer, lymphoma, Kaposi's, cervical ca, RCC, vulvar ca

### **Why is BCG contraindicated in pts w/ renal transplant?**

- **risk of systemic infection**
- likelihood of diminished therapeutic response



## **Chapter 11**

### **• Physiology and Pharmacology of the Renal Pelvis and Ureter •**

---

#### **What is the resting membrane potential of the ureter?**

- -33 to -70mV
  - determined mostly by distribution of  $K^+$  ions across the cell membrane and permeability to  $K^+$
  - inside of cell more -ve than outside
  - greater concentration of  $K^+$  on inside, greater concentration of  $Na^+$  on outside

#### **Describe the events of an action potential inside a ureteral smooth muscle cell.**

- ureteral cell stimulated → if enough cell membrane is depolarized to reach the threshold potential, an AP is generated
- membrane loses preferential permeability to  $K^+$  and becomes more permeable to  $Ca^{2+}$ 
  - $Ca^{2+}$  moves across cell mmb via L-type  $Ca^{2+}$  channels
  - inside of cell becomes less negative, may become positive → overshoot
- ureter maintains its potential (plateau) and then repolarizes due to increase in permeability to  $K^+$ 
  - outward  $Ca$ -dependent  $K^+$  channels

#### **Where are the pacemaker cells of the ureter?**

- near pelvicalyceal border
  - electrical activity arises spontaneously: transmembrane RMP is lower (less -ve) than non-pacemaker cells
  - does not remain constant: slow spontaneous depolarization
  - if spontaneously changing RMP reaches threshold, AP occurs

#### **What are latent pacemakers and where are they located?**

- other areas of the ureter that can act as pacemakers, and are dominated by the primary pacemaker
- located at the UVJ, cause antiperistaltic waves at frequency lower than from upper segment

#### **How is electrical activity propagated from one ureteral cell to another?**

- across areas of close cellular apposition called "intermediate junctions"

#### **What is the conduction velocity in the ureter?**

- 2-6 cm/sec

#### **Compare and contrast the role of calcium in skeletal vs. smooth muscle.**

- skeletal
  - $Ca^{2+}$  acts as a de-repressor
  - troponin and tropomyosin prevent interaction of myosin and actin
  - w/ activation, get increase in SR  $Ca^{2+}$  concentration
  - $Ca^{2+}$  binds to tropomyosin, causing a conformational change that allows actin-myosin interaction
- smooth
  - $Ca^{2+}$  acts as an activator
  - $Ca^{2+}$  binds w/  $Ca^{2+}$ -binding protein calmodulin
  - $Ca^{2+}$ -calmodulin complex activates myosin light chain kinase (MLCK), which phosphorylates myosin
  - P-myosin allows actin to activate myosin Mg-ATPase activity, causing ATP hydrolysis and development of smooth muscle shortening
  - if MLCK is phosphorylated via cAMP (or cGMP) dependent kinase, decreases MLCK activity

#### **Describe the mechanism by which beta-adrenergic activation causes smooth muscle cell relaxation.**

- beta agonist R activates adenylyl cyclase on inner surface of cell membrane
- adenylyl cyclase converts ATP → cAMP (requiring Mg and GTP)
- G protein communicates b/w adenylyl cyclase and beta-agonist R
- cAMP causes reuptake of Ca into stores, preventing stimulation of smooth muscle

#### **What are the different isoforms of NOS?**

## Chapter 11 Questions - Renal pelvis.doc

- NOS converts L-arginine to NO and L-citrulline
- neuronal NOS (nNOS)
  - $\text{Ca}^{2+}$  and NADPH dependent
  - present in neuronal tissues
  - w/ neuronal excitation, there is an increase in  $\text{Ca}^{2+}$  concentration w/i nerves that leads to NO synthesis
- endothelial NOS (eNOS)
  - $\text{Ca}^{2+}$  and NADPH dependent
- inducible NOS (iNOS)
  - NADPH dependent,  $\text{Ca}^{2+}$  independent

### What is ureteral *hysteresis*?

- resting or contractile force developed by the ureter at a given length depends on the direction in which the change in length is occurring and on the rate of length change

### What is ureteral *creep*?

- after application of an intraluminal pressure, the ureter increases in both length and diameter

### What is the role of the parasympathetic nervous system in ureteral function?

- muscarinic cholinergic receptors have been demonstrated in the ureter
- cholinergic agonists have an excitatory effect on ureteral function: methacholine, carbamylcholine, bethanechol
  - increase force and frequency of contractions

### Name 2 anticholinesterases.

- physostigmine and neostigmine: parallel the excitatory effects of ACh and other parasympathomimetics on the ureter

### How does atropine affect ureteral function?

- atropine is a competitive inhibitor of ACh → little direct effect on ureteral activity

### Other than atropine, name 2 other parasympathetic blocking agents.

- methantheline (Banthine) and propantheline (Pro-Banthine)

### What is the role of the sympathetic nervous system in ureteral function?

- ureter contains excitatory alpha- and inhibitory beta-adrenergic receptors
  - NE: primarily  $\alpha$ -agonist: increases ureteral contraction
    - synthesized in the neuron from tyrosine
    - degraded by monoamine oxidase (MAO)
  - isoproterenol  $\beta$ -agonist: decreases ureteral contraction

### What peptides are involved in ureteral function, and how?

- tachykinins
  - released from peripheral endings of sensory nerves
  - **stimulate contractile activity**
- CGRP
  - released from peripheral endings of sensory nerves
  - **inhibit contractile activity**
  - open ATP-sensitive  $\text{K}^+$  channels, causing hyperpolarization w/ blockage of voltage sensitive Ca channels
- capsaicin
  - inhibits at low doses, stimulates at high doses
- VIP, NPY

### How does the muscle in the renal pelvis move urine into the upper ureter?

- calyceal and renal pelvis actively contract w/ relative block of electric activity at UPJ
- as renal pelvic pressure rises, urine is extruded into the upper ureter via contraction wave
  - must have coaptation of the ureteral walls
- baseline ureteral pressure 0-5cm  $\text{H}_2\text{O}$
- ureteral contractions range from 20-80 cm  $\text{H}_2\text{O}$  2-6X/min

### What is the effect of diuresis on ureteral function?

- w/ increasing flow, ureter initially increase peristaltic frequency
- after maximal frequency is reached, further increases in flow cause increased bolus volume

## Chapter 11 Questions - Renal pelvis.doc

- as flow increases, boluses coalesce until finally the ureter fills w/ column of fluid

### How does bladder filling effect ureteral function?

- **pressure inside the bladder during storage is most important**
- w/ bladder filling normally, bladder maintains low filling pressure to prevent ureteral dilation
- w/ increasing bladder pressures and decreasing ability of ureter to empty, ureter will increase its peristaltic frequency
  - pressure w/i bolus of urine must exceed filling pressure of bladder for bolus to cross UVJ
  - ureter decompensates when intravesical pressure > 40 cm H<sub>2</sub>O

### How does the UVJ change in order to facilitate ureteral emptying?

- distal ureter retracts w/i its sheaths: telescoping allows decreased UVJ resistance
- UVJ does not relax

### What are the determinants of obstruction on ureteral function?

- degree and duration of obstruction
- rate of urine flow
- presence of infection

### What is the effect of obstruction on ureteral function?

- increase in ureteral dimension from: increase in intraureteric pressure, increased volume of urine retained
- as ureter fills, peristaltic waves decrease and are unable to coapt the ureteric walls
- after a few hours of obstruction, pressure peaks and then decreases to level slightly higher than normal baseline pressure
- as obstruction persists, increase in ureteral length and diameter (creep)
  - muscle hypertrophy w/ increased contractility occurs
- discoordination of pacemakers that normally coordinate peristaltic activity: incomplete emptying of renal pelvis
- w/ prolonged complete obstruction, total cessation of urine output occurs

### What causes the decrease in ureteral pressure in obstruction?

- reduction in renal blood flow
- decrease in GFR
- fluid resorption in venous and lymphatic systems
- decrease in wall tension

### How is a perfusion study performed?

- cannulate upper tract, infuse fluid at 10 cc/min
- pressure must be measured at steady state, occurring when equilibrium reached b/w flow in and flow out of the system
- bladder must be continuously drained

### What level of pressure is considered normal or abnormal in a perfusion study?

- < 15cm water = nonobstructed
- > 22cm water = clinically significant obstruction
- 15-22 = equivocal

### What extrinsic factors affect pressure readings in a Whittaker study?

- needle size
- tube length and compliance
- viscosity of the perfusing fluid
- temperature
- flow rate

### How does VUR affect ureteral function?

- decreased frequency of ureteric peristalsis
- increased pressure in distal ureter compared w/ normal systems

### How does infection affect ureteral function?

- infection w/i upper tract may impair urine transport
  - toxins inhibit contractions: bacteria and *E. Coli* endotoxin
  - ureteral dilation
  - reduced compliance of intravesical ureter → may allow VUR to occur

## **Chapter 11 Questions - Renal pelvis.doc**

### **What are the determinants of the spontaneous passage of a ureteric stone?**

- size and shape of stone
- areas of narrowing w/i ureter
- ureteral peristalsis
- hydrostatic pressure of column of urine proximally
- edema, inflammation, and spasm of ureter

### **What 2 factors are most important in allowing stone passage?**

- increased proximal hydrostatic pressure
- relaxation of the ureter in area of the stone

### **How does the ureter differ in its response to obstruction in infant vs. adult?**

- more dilation seen w/ obstruction in neonate and young child

### **How does age affect the response of the ureter to beta-adrenergic agonists?**

- decreased relaxation response w/ aging
- decreased synthesis of cAMP

### **How does pregnancy affect ureteric function?**

- hydro occurs during 2<sup>nd</sup> and 3<sup>rd</sup> trimester, R > L
  - starts in 6<sup>th</sup>-10<sup>th</sup> week, in 90% by 26<sup>th</sup>-28<sup>th</sup> week
- increased hydrostatic pressure above pelvic brim
  - no hydro if ureters do not cross pelvic brim (ex: pelvic kidneys)
  - does not occur in animals that walk on all fours: uterus hangs away
- progesterone increases the degree of ureteral dilation → inhibitory effect on ureteric function
  - not the prime factor in dilation

### **What is the management of hydro in pregnancy?**

- examine urine, urine C&S: r/o stone vs. pyelo
- IV hydration, antibiotics
- stent, NT

### **How does histamine affect ureteric function?**

- histamine has a dual action on smooth muscle
  - releases catechols from sympathetic nerve endings → may cause contraction
  - acts directly on R w/i smooth muscle
- **overall has excitatory effect on smooth muscle, mediated by H<sub>1</sub> receptors**
  - blocked by H<sub>1</sub> receptors mepyramine and dimethindine
  - antihistamines (Benadryl) inhibit the effects of histamine on ureter
- H<sub>2</sub> agonists cause relaxation

### **How does serotonin affect ureteric function?**

- conflicting studies

### **How do narcotics affect ureteric function?**

- mixed: morphine and Demerol increase or has no effect on ureteric tone
  - major effect via CNS actions for pain perception

### **How do NSAIDs affect ureteric function?**

- PGs cause vasodilation
- NSAIDs prevent PG formation, decreasing glomerular pressure, ureteric pressure and wall tension
  - potentially damaging to renal function

### **How do CCBs affect ureteric function?**

- blockage of L-type calcium channels by verapamil, diltiazem, or nifedipine **inhibit ureteric activity**

### **How do potassium channel openers affect ureteric function?**

- cromakalim: hyperpolarize smooth muscle membranes and **inhibit activity**

## **Chapter 11 Questions - Renal pelvis.doc**

### **How do endothelins affect ureteric activity?**

- endothelins are potent vasoconstrictors: ET-1, ET-2, ET-3 → R are ET<sub>A</sub>, ET<sub>B</sub>, and ET<sub>C</sub>
- primarily ET<sub>A</sub> subtype receptors in ureter: stimulate contractions

### **How do antibiotics affect ureteric activity?**

- ampicillin causes relaxation of ureter and antagonizes stimulatory effects of barium, histamine, serotonin
- gentamycin has spasmolytic effects





## Chapter 12

### • Pathophysiology of Urinary Tract Obstruction •

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#### **What is the definition of obstructive nephropathy?**

- damage to the renal parenchyma that results from an obstruction to the flow of urine anywhere along the GU tract

#### **What are the possible causes of obstructive uropathy?**

- Renal
  - Congenital: PCKD, renal cyst, UPJO, peripelvic cyst
  - Neoplastic: Wilms', RCC, TCC of renal pelvis, MM
  - Inflammation/Infection: TB, echinococcus, fungus ball
  - Metabolic: stone
  - Misc: sloughed papillae, trauma, RAA
- Ureter
  - Congenital: stricture, ureterocele, VUR, ureteral valve, ectopic kidney, pre-ureteral vena cava, prune-belly
  - Neoplastic: ureteral ca, mets
  - Inflammx/infection: TB, schistosomiasis, abscess, ureteritis cystica, endometriosis, RPF, tubo-ovarian abscess
  - Misc: pelvic lipomatosis, AAA, radiation, lymphocele, trauma, urinoma, pregnancy, ligation intra-op
- Bladder
  - Neoplastic: TCC
  - Misc: neurogenic bladder
- Urethra
  - Congenital: PUV, phimosis, urethral stricture, hypospadias, epispadias, hydrocolpos
  - Neoplastic: prostate ca, urethral ca, penile ca
  - Inflammation: prostatitis, paraurethral abscess
  - Misc: BPH

#### **How can one classify obstructive uropathy?**

- acute vs. chronic
- unilateral vs. bilateral
- intrinsic vs. extrinsic
- complete vs. partial

#### **What are the sx of GU obstruction?**

- Acute
  - unremitting flank pain +/- radiating to groin or thigh
  - N/V
  - fever, chills if infected
  - anuria (if BUO)
- Chronic
  - Bilateral
    - increase in abdominal girth
    - ankle edema
    - malaise
    - anorexia
    - h/a
    - weight gain
    - fatigue
    - SOB
    - uremic sx: mental status change, tremors, GIB
  - Unilateral
    - intermittent flank pain
    - flank pain w/ diuresis (Dietl's crisis)



## Chapter 12 Questions - Obstruction.doc

- gross hematuria
- increase in urine output (decreased renal concentrating ability)
- asymptomatic if slow onset (ex: MUO)

### What are the signs of GU obstruction?

- abdominal mass (rare)
- volume overload: edema, pulm congestion, htn
- urinalysis: hematuria, proteinuria, crystalluria, pyuria, casts
- urine lytes: elevated urine Na, decreased urine osmolality, decreased urine-to-plasma creatinine ratio
  - acute obstr: decreased urine Na, increased osmolality
- blood: increased urea, Cr, K, acidosis
  - remember intraperitoneal bladder rupture will increase Cr w/o renal failure
- sepsis if infection

### How can one diagnose obstructive uropathy?

- IVU
  - Acute: obstructive nephrogram, delay in filling, dilation of collecting system, fornix rupture w/ extravasation
  - Chronic: ureteral dilation and tortuosity, parenchymal thinning, calyceal crescents, soap-bubble nephrogram, standing column of contrast
- US
  - dilated renal collecting system
  - renal parenchymal thinning
- Diuretic Renography
- Whitaker test: gold standard
  - pressure < 15cm water not obstructed, >22cm water obstructed, 15-22 equivocal
- Duplex Doppler US and RRI
- CT/MR
  - CT w/o contrast more sensitive for ureteric stones than IVU
  - CT gives more information on extrinsic causes of obstruction
  - CT w/ contrast gives functional information
  - MR urography accurate to dx obstruction, but stones seen poorly → indicated in pts w/ renal failure or w/ contrast allergy
    - high cost, longer time to do study, cannot see stones

### What will cause a false-negative or false +ve result on US in setting of obstruction?

- False -ve
  - acute onset → prior to development of hydro
  - intrarenal collecting system
  - dehydration
  - misinterpretation of caliectasis as renal cortical cysts
- False +ve
  - capacious extrarenal pelvis
  - parapelvic cysts
  - VUR
  - high urine flow rate

### How does one perform a diuretic renogram to dx obstruction?

- pts must be well hydrated
- no need for Foley if pt can void spontaneously → Foley if retention
  - will ensure adequate bladder drainage
  - reduces false +ve results
  - decreases radiation dose to bladder and gonads
- increase diuretic dose in pts that have poor function
- timing of diuretic
  - F+20: give radiopharmaceutical agent, then IV Lasix 20 min later
  - F-15: give Lasix prior to tracer

### What is signified on diuretic renography by an increasing accumulation of tracer then rapid emptying after diuretic administration?

- dilation w/o obstruction

## Chapter 12 Questions - Obstruction.doc

### How does one distinguish inability to excrete contrast vs. partially obstructed system?

- F-15 study
  - diuretic administered first
  - equivocal diuretic response converted to washout response
  - normalizes partially obstructed curve

### What is the definition of the renal resistive index?

- $RI = ([\text{peak systolic velocity}] - [\text{lowest diastolic velocity}]) / \text{peak systolic velocity}$
- normal  $< 0.7$ , obstruction if  $> 0.7$ , significant if RI of one kidney 0.1 greater than the other
- controversial whether it can be used to dx acute obstruction

### What are the secondary signs of obstruction on CT?

- hydroureter, hydronephrosis, perinephric stranding, periureteral edema, renal swelling

### What are the potential causes for RPF?

- Drugs: **methysergide**, hydralazine, reserpine, haldol, LSD, methyldopa, beta blockers, ergotamine alkaloids, phenacetin, amphetamines
- Chemicals: avitine, methacrylate, talc
- Retroperitoneal tumours
- Inflammatory processes: ascending lymphangitis, IBD
- Hemorrhage: abdo/pelvic surgery, ruptured viscus, HSP w/ hemorrhage
- Periarteritis: **AAA**, atherosclerosis w/ inflammation, collagen vascular disease
- Infection: gonorrhea, TB, UTI, syphilis
- Radiation
- Misc: sarcoid, biliary tract disease, endometriosis
- GI

### What are the sx of RPF?

- backache, abdo/flank pain
- weight loss
- N/V
- edema
- malaise
- GI bleed
- anuria

### What is seen on CT in RPF?

- centrally located soft tissue mass encasing the great vessels, from renal hilum to bifurcation of aorta
- medial deviation of ureters, proximal hydro

### What is the management of RPF?

- labs: BP, BUN, Cr, ESR, gamma globulin, CBC
- imaging
  - IVP if normal renal function
  - US if poor function
  - retrograde: confirm level and extent of ureteral involvement
  - CT: mass, dilation
- place ureteral stents or NT
- laparotomy or biopsy to r/o malignancy
  - steroids if inflammation present on biopsy
- bilateral ureterolysis
- stop medications that may cause RPF

### What is pelvic lipomatosis?

- benign condition of mature unencapsulated fat in the retroperitoneum
- etiology unknown
- produces a characteristic "pear-shaped", "teardrop-shaped", or "gourd-shaped" bladder

### What groups of patients get pelvic lipomatosis?

## Chapter 12 Questions - Obstruction.doc

- mostly males, mostly aged 25-55, 33% white
  - young stocky obese males w/ sx of pelvic pain, hematuria, LUTS, htn
  - old men > 60 yrs discovered during w/u for LUTS

### What are the clinical and radiologic findings of pelvic lipomatosis?

- Clinical
  - voiding sx: freq, dysuria, nocturia
  - pain: tenderness, LBP, pelvic pain, pain on ejaculation
  - lower extremity thrombophlebitis
  - constipation: other GI sx are rare
  - htn
  - SP mass
  - high-lying prostate
- Radiologic
  - CT: easily diagnoses pelvic lipomatosis → can r/o other causes of pear shaped bladder
  - MR: little advantage over CT
  - cysto: difficult due to elongated urethra → may see cystitis glandularis

### What is the tx of pelvic lipomatosis?

- **weight loss**
- ureteral stent, NT
- surgical removal of fatty pelvic tissue → ++ complications
- reimplantation
- urinary diversion

### What are the causes of a pear-shaped bladder?

- pelvic lipomatosis
- perivesical hematoma, urinoma, abscess
- iliopsoas hypertrophy
- lymphoma
- carcinoma
- IVC obstruction
- lymphocele
- iliac aneurysm
- bilat THR w/ extruded cement
- pelvic fibrosis
- pancreatic pseudocysts
- gross prolapse
- edema
- lipoplastic lymphadenopathy
- ureteral compression balloons

### What are the causes of pelvic pain in adolescents?

- Acute
  - PID, ectopic pregnancy, adnexal torsion, ruptured ovarian cyst, hemorrhagic corpus luteum cyst, appy, gastro, bowel obstruction, UTI, stone, pyelo
- Chronic-cyclic
  - dysmenorrhea, Mittelschmerz, endometriosis, torsion, obstructive Mullerian duct anomalies
- Chronic-noncyclic
  - endometriosis, adhesions, ovarian mass, IBS, constipation, IBD, lactose intolerance, bowel infection, stone, MSK, psych

### What is endometriosis?

- presence of functional endometrial tissue outside its normal location in the uterus
  - endometriosis of GU tract usually found in bladder: 75-80% of cases
- most common form of endometriosis of the ureter is extrinsic obstruction
  - **most common site of ureteric obstruction in endometriosis at ureterosacral ligaments**
- sx: cyclical flank pain, LUTS, dysuria, UTIs, hematuria → present in < 50% of pts
  - sx more common in pts w/ intrinsic disease rather than extrinsic compression

## **Chapter 12 Questions - Obstruction.doc**

### **What is the management of endometriosis?**

- imaging
  - image kidneys in all pts w/ endometriosis
  - US, IVP if high index of suspicion → may be able to see intrinsic disease
- normal renal fn w/ mild hydro, normal renal scan = hormonal treatment
  - Danazol (anti-estrogen), gonadotropin-releasing hormone agonists (leuprolide)
- significant hydro, periureteral disease, and fibrosis = surgical treatment
  - TAH and BSO vs. USO (if further pregnancies desired)

### **What is ovarian remnant syndrome?**

- remnants of ovarian cortex are left behind after BSO, and they **become functional and cystic**
- liquor folliculi may cause fibrosis, causing ureteral obstruction
- sx: cyclical pelvic pain, constipation, LUTS, flank pain
  - pain is dull, nonradiating, localized to area of mass
- US can usually detect the mass
- treatment: mass excision, ureterolysis, stents preop if needed

### **What are the mechanisms for obstruction in uterine prolapse?**

- kinking of the ureter
- intramural stretching of the bladder wall w/ compression of the intramural ureter
- constriction of the ureter by the uterine artery as it is stretched
- compression of the ureters against the soft tissues of the pelvis
- constriction of the ureters by the cardinal ligaments

### **Where is the ureter most commonly injured during OR?**

- at the pelvic brim

### **What are the RF for ureteral injury intra-op?**

- previous operations in the pelvis
- operating at the pelvic brim
- distorted anatomy at the pelvic sidewall
- removal of an adnexa after a previous TAH
- removal of ovarian ca, abscess, or endometriomas
- repair of bladder injuries

### **What are the signs/sx of ureteral injury post-op?**

- flank or abdo pain
- persisting fever
- drainage from the vagina or wound
- N/V
- prolonged ileus
- anuria
- leukocytosis
- **identification of ureter on path report!!**

### **What is the management of the injured ureter?**

- intraop or w/i 3-5 days post-op: immediate repair → deligation +/- ureteroureterostomy, reimplant
  - contraindicated in the septic pt or one who is a poor surgical risk → get NT
- after 5-7 days: ureteral stent or NT, plan future treatment

### **What are the 2 main arteries likely to cause ureteral obstruction or disease?**

- aorta or iliac
- sx: pulsatile mass, abdominal bruit, unequal peripheral pulses

### **How often are the ureters involved in AAA?**

- 15-30%
  - only 1/10<sup>th</sup> as common in iliac aneurysm

### **What are the potential causes for the medial deviation of the ureter seen during aortic disease?**

- leakage of small amounts of blood

## **Chapter 12 Questions - Obstruction.doc**

- stimulates perianeurysmic fibrosis
- atherosclerosis from AAA causes fibrosis

### **Where is the most common site for ureteric obstruction in iliac aneurysm?**

- as the ureters cross over the iliac vessels

### **What is the most common presentation of iliac artery aneurysm?**

- leg pain associated w/ ipsilateral neurologic deficit
- pulsatile mass
- hydro + nonvisualization of ipsilateral kidney on IVP

### **What are the urologic sx seen after vascular repair of AAA?**

- present in 56%
  - flank pain: most common
  - anuria, LUTS, renal failure, hematuria, htn, chyluria, urocutaneous fistula
- most present in 1<sup>st</sup> 12 mo after repair

### **What is the treatment of ureteric obstruction after vascular repair?**

- Surgical
  - NT, ureterolysis, ureteral resection, ureteroureterostomy, trans u-u
- Medical
  - steroids, none
- potential for infection of graft: may want to reposition graft or ureter laterally or intraperitoneally

### **What is ovarian vein syndrome?**

- old term for puerperal ovarian vein thrombophlebitis

### **What is puerperal ovarian vein thrombophlebitis?**

- inflammation and clot of R ovarian vein
  - occurs in 1 of 2000-3000 pregnancies
- sx: N/V, abdo distension, abdo pain, guarding
  - can cause ureteral obstruction
- diagnose w/ CT
- treat w/ antibiotics +/- heparin

### **What is the mechanism of formation of circumcaval ureter?**

- normally, the IVC is formed infrarenally from supracardinal vein and suprarenally from subcardinal vein
  - subcardinal vein → supracardinal vein → posterior cardinal vein
- if infrarenal IVC formed from subcardinal vein ventral to ureter → retrocaval ureter
  - subcardinal vein → posterior cardinal vein

### **How can one classify circumcaval ureter?**

- Type 1: more common S "fish-hook" form
  - moderate to severe hydro
- Type 2: sickle-shaped curve w/ obstruction at lateral margin of IVC
  - mild hydro
  - compression from psoas, spinal column, and IVC

### **What are the indications to relieve ureteric obstruction?**

- UUO
  - pain unrelieved by analgesics
  - fever
  - persistent N/V
  - high-grade obstruction
- BUO
  - same for UUO plus:
  - elevated BUN/Cr
  - uremic sx
  - hyperkalemia

## Chapter 12 Questions - Obstruction.doc

### What % of function must a kidney have to be considered salvageable?

- 10% of total renal function
  - must fix obstruction (stent) before one can interpret renal nuclear medicine studies → repeat after stent to assess recovery

### What is the treatment for UUO?

- Meds
  - IV narcotics
  - NSAIDs: will decrease renal blood flow, ureteric/renal pelvic muscle tone and contractions
    - as effective as narcotics in treatment of colic
  - CCB: may be useful in chronic UUO

### What glomerular and tubular changes occur in UUO?

- decrease in GFR
- decrease in concentrating ability
  - associated w/ inability of CCT to respond to ADH or cAMP stimulation
    - decreased expression of aquaporin
  - partial obstruction: decrease in sodium and water excretion prior to tubular damage, w/ increase in urine osmolality
    - significant water loss only if GFR preserved
- impaired distal hydrogen ion secretion
  - impaired urinary acidification
- higher bicarbonate reabsorption rate
- decreased phosphate excretion after UUO release
- decreased K secretion excretion after UUO release

### How does RBF change in UUO?

- triphasic change measured during 18hrs
  - 1<sup>st</sup> phase: rise in ureteral pressure and RBF lasting 1-1.5 hrs
    - afferent arteriole dilation due to eicosanoid vasodilation → designed to maintain GFR
  - 2<sup>nd</sup> phase: decline in RBF w/ continued increase in ureteral pressure until 5<sup>th</sup> hour
    - efferent arteriole constriction
  - 3<sup>rd</sup> phase: decline in RBF w/ decreased ureteral pressure from 5<sup>th</sup>-18<sup>th</sup> hour
    - afferent arteriole constriction – eicosanoid TxA<sub>2</sub> may be involved
    - decrease in perfusion of superficial cortical tissue, increase in perfusion of juxtamedullary glomeruli after 24h
      - ◆ due to increase in renin in outer cortex relative to inner medulla
    - ultimately, GFR decreases by ~75% from baseline at 24h
- marked decrease in perfusion of superficial cortical tissue and increase in perfusion of juxtamedullary glomeruli after 24h of UUO

### How does the RAA system change during UUO?

- elevated plasma renin seen during UUO

### How does NO affect RBF?

- NO has a role in diminishing preglomerular vascular resistance after UUO
  - NOS inhibitor given before UUO decreases initial rise in RBF

### What mediators have vasoactive effects on the glomerulus?

- Afferent
  - Vasodilation: PGE<sub>2</sub>, PGI<sub>2</sub>, NO, ANP
  - Vasoconstriction: ANGII, endothelin, PAF
- Efferent
  - Vasodilation: PGI<sub>2</sub>, NO
  - Vasoconstriction: ANGII, endothelin, PAF, ANP

### Describe the anatomic changes in the kidney after obstruction.

- Gross
  - dilation of collecting system: decreased ability to dilate if intrarenal pelvis
  - enlarged, normal, or atrophic kidney
  - with time, enlarged collecting system compresses renal papilla, thinning tissue b/w calyces → coalesce
  - increased renal weight and pelvic fluid volume up to 4 months

## Chapter 12 Questions - Obstruction.doc

- Microscopic
  - **hyalinization** and connective tissue proliferation: collagen seen by 7 days after UUO, increases up to 32 days
    - increase in collagen type III
    - increase in TIMPs, which inhibit metalloproteinases (normally degrades collagen), allowing collagen to be laid down
    - glomeruli resistant to change: only slight thickening
  - flattening of tubules
  - **hemorrhage and necrosis** after 24h in papillae and fornices
  - tubular proliferation peak by day 10, interstitial proliferation peak by day 10-20, and 2<sup>nd</sup> peak by day 75
  - tubular **apoptosis** peak by day 25, interstitial apoptosis peak by day 75
  - **macrophage infiltration**
  - **transformation of fibroblasts to myofibroblasts**
  - increase in TGF- $\beta$

### How does TGF- $\beta$ change in UUO?

- increase in TGF- $\beta$ : profibrotic cytokine

### How does the angiotensin receptor affect the presence of fibrosis in UUO?

- ACEi: decreases ANGII synthesis → decreases collagen, decreases TGF- $\beta$ , decreases macrophages
- AT1 R knockout: decreased fibrosis, etc

### In canine models, how does UUO affect renal function?

- intrapelvic pressure increases after obstruction and decreases by day 14
- muscular hypertrophy
- RBF unchanged by 1 week, decreased by 4-5 weeks at outer cortex
- 100% reversible by 2 weeks, 31% reversible by 28 days, 8% reversible by 60 days

### How does RBF change in BUO?

- triphasic response not seen
  - RBF increases after the 1<sup>st</sup> 90 minutes, but to a lesser degree compared w/ UUO
  - increased renal vascular resistance compared w/ UUO
  - medullary BF even further compromised than unilateral
  - by 24h, RBF and renal vascular resistance are equal to UUO

### How does ureteral pressure change in BUO?

- ureteral pressure is higher than in UUO
- progressive increase in pressure for 1<sup>st</sup> 4.5hrs
- after 4.5h, ureteral pressure remains elevated until 24-48h (in UUO, ureteral pressure declines to N by 24h)

### How does the GFR change in BUO?

- BUO causes preglomerular vasodilation, then postglomerular vasoconstriction → remains in this state
  - caused by ANP, due to increased intravascular volume
  - like being stuck in 2<sup>nd</sup> phase of UUO
- GFR significantly decreased by 48h

### How does ANP mediate its natriuretic and diuretic effects on the kidney?

- increase in GFR via afferent arteriole vasodilation and efferent arteriole vasoconstriction
- increase in glomerular capillary ultrafiltration coefficient
- inhibition of the glomerular-tubular feedback mechanism

### How does ANP change in ureteric obstruction?

- elevated ANP after 24h of BUO, not after 24h UUO (in rats)
  - determined primarily by intravascular volume

### What tubular changes occur in BUO?

- enhanced increase in K excretion after the release of BUO
  - increase in absolute K excretion and fractional excretion of K
- impaired ability to acidify the urine and lower the pH in response to acidemia during BUO
  - inability to secrete H ion against a gradient
- ability to concentrate urine impaired after relief of BUO
  - overall increase in total solute excretion

## Chapter 12 Questions - Obstruction.doc

- inability of thick ascending limb to reabsorb sodium  
→ decreases tonicity of medullary interstitium and reabsorption of water

### Where are the highest density of ANP receptors?

- in inner medullary collecting duct

### Describe the recovery of renal function in UUO in animal models of obstruction.

- full recovery after 7 days of obstruction seen 2 weeks after obstruction reversed
- 14d of obstruction: permanent decline in renal function to 70% of control, by 3-6mo
- some function seen in kidneys obstructed for 4 weeks (30%)
- no function if obstruction beyond approx. 6 weeks

### What are the possible mechanisms by which obstruction may impair urine concentrating ability?

- diminished medullary interstitial hypertonicity  
→ "washout" of solute from interstitium (from increased medullary blood flow)  
→ destruction of papillae and long loops of Henle in chronic obstruction  
→ decreased absorption of NaCl by ascending limb (due to defect in tubular transport of NaCl or decreased delivery of NaCl to ascending limb)
- failure of osmotic equilibration b/w collecting duct and medullary interstitium  
→ rapid flow rate in collecting duct (azotemia causes high solute load per nephron)  
→ relative water impermeability of collecting duct due to ADH insensitivity

### What is postobstructive diuresis?

- polyuria that occurs after the relief of BUO or obstruction of a solitary kidney

### How can one classify postobstructive diuresis?

- physiologic: caused by retained urea, sodium, water
- pathologic: caused by impairment of concentrating ability or sodium reabsorption
- iatrogenic: administration of glucose containing fluids → tubular max for glucose exceeded

### What are the sx of postobstructive diuresis?

- chronic obstruction, edema, CHF, htn, weight gain, azotemia, uremic encephalopathy

### How does one monitor a patient for postobstructive diuresis?

- follow VS q2h
- follow UO q2h
- electrolytes q12h → remember to follow  $Mg^{2+}$
- urine lytes
- daily weight
- free access to fluids  
→ reduce IV glucose containing fluids if applicable
- if low risk: follow urine
- if moderate risk (volume overload and azotemia): follow VS and urine
- if high risk: (volume overload, azotemia, mental confusion): spot check urine for osmolality, Na, K  
→ replace  $\frac{1}{2}$  urine output hourly w/ D5  $\frac{1}{2}$  NS
- if iatrogenic diuresis, reduce glucose containing fluids
- if diuresis persists w/ low urine osmolality → pathologic concentrating defect  
→ administer D5 $\frac{1}{2}$ NS to supplement sodium and allow GFR to recover  
→ pathologic sodium loss (sodium wasting nephropathy): need ++ sodium replacement until pt stabilizes

### How often does htn occur in obstruction?

- UUO: 20-30%
- BUO: 75%

### What is the definition of polyuria?

- urine output > 3L/day in pt not drinking large amounts of urine

### What are the causes of polyuria?

- Water diuresis



## Chapter 12 Questions - Obstruction.doc

- decreased ADH
  - excessive intake of hypotonic fluid
  - psychogenic polydipsia
  - ADH inhibitors: alpha-agonists, EtOH, opioids, Dilantin
- thirst
  - hypercalcemia
  - K depletion
  - hyperreninemia
  - organic primary polydipsia
- central DI
  - idiopathic
  - neoplastic, infiltrative, vascular, inflammatory, trauma
- Cold diuresis (impaired response to ADH)
  - hereditary NDI
  - acquired NDI
    - hypokalemia, hypercalcemia, sickle cell
    - chronic tubulointerstitial disease: obstructive nephropathy, amyloid, PCKD, MCK, Sjogren's
  - cold diuresis
  - meds: Li, methoxyflurane, amphotericin B
- Solute diuresis
  - Nonelectrolyte
    - Urea
      - ◆ metabolic: hypercatabolism, high protein diet
      - ◆ renal disease: postobstructive diuresis, diuretic phase of ATN, post-transplant diuresis
    - Glucose: DM, renal glucosuria, D5W infusion
    - Mannitol
    - Glycerol
    - amino acids
  - Electrolyte
    - NS infusion or ++ salt intake
    - diuretics
    - increased ANP secretion
    - hypoaldosteronism
    - renal disease: impaired tubular reabsorption
      - ◆ salt-losing nephritis
      - ◆ post-obstructive diuresis
      - ◆ diuretic phase of ATN
      - ◆ post-transplantation diuresis
      - ◆ chronic tubulointerstitial disease
- Mixed water-solute diuresis
  - combined uncontrolled DM and CRF
  - postrelief of obstructive nephropathy



### Chapter 13

## • Management of Upper Urinary Tract Obstruction •

---

### What is the etiology of UPJ obstruction?

- Intrinsic
  - aperistaltic segment of ureter: normal spiral muscle replaced by abnormal longitudinal muscle or collagen
    - due to interruption of circular development of UPJ or alteration of collagen development
    - muscle fibers become widely separated and attenuated → leads to functional discontinuity of muscular contractions
  - congenital valvular mucosal folds: "Östlings folds"
    - due to differential growth rates of ureter and body of child: not obstructive, disappear w/ linear growth
  - kinks or valves produced by infoldings
  - polyps
  - ureteral stricture
  - urothelial malignancy
  - stones
  - postinflammatory or postop scarring
- Extrinsic
  - compressing vessel: seen in 1/3 → cross the ureter **posteriorly**
  - external adhesions
  - high insertion of ureter into renal pelvis: may be a secondary phenomenon seen
- Secondary to VUR (10% of cases)

### How does UPJO present?

- infants: asymptomatic
  - may have palpable mass
- children: most have sx
  - episodic flank or upper abdominal discomfort
  - N/V, cyclic vomiting
  - hematuria: 25%
    - after minor abdo trauma: due to disruption and rupture of mucosal vessels in dilated collecting system
  - htn
- adults
  - intermittent abdo/flank pain
  - N/V
  - hematuria: spontaneous, associated w/ minor trauma
  - htn
  - renal failure

### How does one dx UPJO?

- US: initial study
  - UPJO: large medial sonolucent area w/ smaller surrounding areas (calyces), connected to central area
  - MCDK: random distribution of sonolucent areas, little solid tissue seen
- IVP
  - give 0.3-0.5mg/kg
  - if equivocal, repeat at time when pt is symptomatic
- CT: often done as initial study
- renal scan: no uptake on DTPA if UPJO, good uptake in UPJO (even if only cortical rim remains)
  - **all kidneys that function on scans will improve w/ relief of obstruction**

### What is the role of retrograde pyelogram in the workup of UPJO?

- performed at the time of OR to r/o UVJO, and to prevent UTI in the face of obstruction

## Chapter 13 Questions - Obstruction management.doc

- NT if retrograde unsuccessful, or for infants/neonates

### What are the indications for intervention in UPJO?

- **presence of sx** associated w/ obstruction
- impairment of overall **renal function**
- development of **stones** or **infection**
- **hypertension**
- **solitary kidney**
- **bilateral** disease

### What is the success rate for endopyelotomy?

- not comparable w/ open pyeloplasty
  - overall success 73%
  - 42% success if crossing vessel (85% without)
  - 60% if high degree of obstruction
  - 81% if low grade obstruction
- perc endopyelotomy: 85-90%
- cautery wire balloon endopyelotomy: 75-80%
- ureteroscopic endopyelotomy: 80-87%

### When should nephrectomy be considered in UPJO?

- nonfunction of involved renal unit on both radiographic and radionuclide studies: thin shell of parenchyma
  - may place NT/stent if salvagability unclear
- in patients that have extensive stone disease w/ chronic infection and significant loss of function w/ N contralateral kidney
- failure at multiple previous attempts
- limited life expectancy

### What are the contraindications to percutaneous endopyelotomy?

- long segment (>2cm) of obstruction
- active infection
- untreated coagulopathy
- crossing vessels: relative, as will decrease chance for success

### Describe the technique of endopyelotomy.

- investigate comorbidities, treat UTI (stent if necessary), informed consent
- gain percutaneous access: midposterior or superolateral calyx is chosen
- tract is dilated, nephroscopy is performed
- pass wire across UPJ, either from below or above
  - cannot perform endopyelotomy without wire across UPJ
- pass 2<sup>nd</sup> safety wire across UPJ
- remove any associated stones
  - prior to endopyelotomy: fragments may migrate into periureteral tissue
- incise ureter out to periureteral fat **posterolaterally**
  - vessels are uncommon in this area
  - Collins knife or acorn tip Bugbee electrode
- place 14/7 endopyelotomy stent → may be done at the time of passing the 1<sup>st</sup> wire
  - place 10/7 endopyelotomy stent if difficult
- leave NT x 48h, perform nephrostogram
- postop care
  - avoid strenuous activity x 8-10days
  - leave stent x 4 weeks
  - IVP +/- diuretic renogram 1 month after stent out
  - follow q6mo x 2-3 years

### What are the options for a failed endopyelotomy?

- lap or open pyeloplasty → generally offered to anyone who has failed an endoscopic approach
- retrograde endopyelotomy
- repeat perc endopyelotomy
- ureterocalycostomy

## Chapter 13 Questions - Obstruction management.doc

### What are the complications of percutaneous endopyelotomy, and their treatments?

- hemorrhage: bed rest, hydration, transfusion
  - less of a problem, as thinner renal parenchyma, collecting system is dilated
  - do not irrigate NT: allow it to tamponade
  - angiographic embolization if unsuccessful → almost never have to open to control bleeding
- infection: 2<sup>nd</sup> generation cephalosporin on call to OR
  - prophylactic abx while stent is in situ
- persistent obstruction
  - continued nephrostomy drainage x few days
  - change stent as necessary over wire

### What are the contraindications to the cautery wire balloon endopyelotomy?

- long length of obstruction
- **associated upper tract stones** → does not allow for concomitant management
- ?presence of crossing vessels

### Describe the technique and the postop care of cautery wire balloon endopyelotomy.

- retrograde pyelogram to define anatomy of UPJ
  - define insertion of UPJ to determine direction needed for incision
- stiff nonconducting wire passed retrogradely across UPJ
- cautery wire passed w/ cutting wire positioned appropriately → rotation of device impossible in place
- 3cc balloon inflated: waist of UPJO seen
- incision performed
- balloon filled w/ another 1-2cc of dilute contrast, cut x 2-3 seconds
- balloon kept inflated x minutes → may see extravasation of contrast
  - ureteroscopy if do not see extravasation, so as to ensure adequate incision
- balloon removed, wire still in place
- stent passed over wire: 10/7 endopyelotomy stent
- Foley x 24-48h
- Postop
  - follow in house x 24h, Foley removed next morning
  - daily dose antibiotics
  - stent x 1 month

### What are the complications of cautery wire balloon endopyelotomy?

- mostly vascular
  - depth of incision is not controllable
  - vascular injury requires angio and embolization
- ureteral avulsion
- stent-related problems
- detachment of the cutting wire
- failure of balloon inflation

### What is the advantage of ureteroscopic endopyelotomy?

- allows for direct visualization of UPJ
- properly sited, full-thickness endopyelotomy incision

### What are the contraindications to ureteroscopic endopyelotomy?

- long areas of obstruction
- upper tract stones

### Describe the technique of ureteroscopic endopyelotomy.

- retrograde pyelogram to identify location of the ureteral insertion into the UPJ
- pass wire across UPJ (+ 2<sup>nd</sup> wire if flexible ureteroscope used)
- pass ureteroscope along wire to UPJ: can use 6.9F semi-rigid
- renal pelvis drained to allow movement across UPJ
- 365um laser fiber inserted, UPJ incised posterolaterally
  - laser set to 1.2J and 10-15Hz
- incision gradually deepened into peripelvic and periureteral retroperitoneal space
  - small areas of bleeding taken care of by defocusing laser

### Chapter 13 Questions - Obstruction management.doc

- 10/7 endopyelotomy stent passed over the remaining wire
- Foley left overnight
- stent left x 1 month
- IVP 4-6 weeks after stent out, follow x 2 years

#### What are the options for formal pyeloplasty?

- dismembered pyeloplasty
- flap procedures
  - Foley Y-V plasty: not used much → use dismembered pyeloplasty
  - Culp-DeWeerd spiral flap: use if longer stricture
  - Scardino-Prince vertical flap: not used much → use dismembered pyeloplasty
- Davis intubated ureterotomy: not used much → use spiral flap
- "salvage" procedures
  - ureterocalicostomy: use for failed pyeloplasty, or w/ small intrarenal pelvis
- laparoscopic pyeloplasty

#### What are the options for incisions for pyeloplasty?

- anterior extraperitoneal approach: minimal mobilization
- anterior transperitoneal approach: for bilateral disease
- dorsal lumbotomy: best for thin pts, no previous ipsilateral surgery
- extraperitoneal flank approach
  - subcostal
  - 12<sup>th</sup> rib

#### When is preoperative drainage of a kidney needed in UPJO?

- **infection** associated w/ obstruction
- **renal failure** from obstruction in solitary kidney or bilateral disease
- **pain** from obstruction

#### What are the advantages and disadvantages of dismembered pyeloplasty?

- Advantages
  - can be used regardless of location of ureteral insertion
  - allows reduction of a redundant pelvis
  - allows straightening of a lengthy or tortuous ureter
  - allows for anterior or posterior transposition of the UPJ
  - allows excision of faulty UPJ
- Disadvantages
  - poorly suited to lengthy or multiple proximal ureteral strictures, or inaccessible intrarenal pelvis

#### Describe the technique of dismembered pyeloplasty.

- identify proximal ureter in retroperitoneum
- dissect ureter superior to renal pelvis, leaving ++ periureteral tissue
- place stay stitch in proximal ureter
- excise UPJ
- spatulate proximal ureter on lateral side
- anastomosis performed w/ running or interrupted absorbable sutures placed full thickness
- reduction performed if large redundant pelvis
- **JP or Penrose mandatory**

#### Describe the Foley V-Y plasty.

- expose pelvis and proximal ureter
- create widely based triangular or V-shaped flap, w/ base of V on dependent medial aspect of the renal pelvis, apex at UPJ
- incision in ureter should traverse area of stenosis and extend for several mm
- Potts or Metz to complete flap and ureterotomy
- stent placed
- posterior wall reapproximated, then anterior wall

#### What is the specific contraindication to a Foley V-Y plasty?

- when transposition of lower pole vessels is required

## Chapter 13 Questions - Obstruction management.doc

- little value when reduction of renal pelvis is required

### Describe the Culp-DeWeerd spiral flap.

- spiral flap outlined w/ broad base
  - base should be lateral to UPJ to preserve blood supply to flap
  - ratio of flap length to width should not exceed 3:1
  - flap will shrink: make larger than expected

### When is the best time to use a Culp-DeWeerd spiral flap?

- if large extrarenal pelvis in which the ureteral insertion is already dependent
- if UPJO has **relatively long segment of proximal ureteral narrowing** or stricture

### Describe the Scardino-Prince vertical flap.

- similar to spiral flap, except base of flap situated more horizontally on dependent aspect of renal pelvis b/w UPJ and renal parenchyma
- straight incisions vertically to create flap

### Describe the technique of the Davis intubated ureterotomy.

- best combined w/ spiral flap, w/ long proximal defects
- ureterotomy carried completely through long strictured area
- nephrostomy tube drainage routinely used
- distal ureterotomy left open
- nephrostogram in 6-8 weeks

### Describe the technique of a ureterocalycostomy.

- ureter isolated in retroperitoneum and dissected proximally
- **parenchyma overlying lower pole calyx resected**
  - cannot do simple nephrotomy over an inferior calyx → secondary stricture occurs
- proximal ureter spatulated, anastomosis using interrupted sutures
  - each suture placed and left untied until final one in place
- anast protected w/ omental flap
- IVP 1mo after stent removed
- Postop
  - drains removed 24-48h after drainage stops
  - remove stent 4-6 weeks postop
  - nephrostogram after 1 week postop
  - if no stent and drainage persists beyond 7-10 days, pass retrograde stent

### What are the specific contraindications to lap pyeloplasty?

- long segment of obstruction
- pyelocalyceal stone that cannot be accessed at time of OR

### Describe the technique of lap pyeloplasty.

- cysto and retrograde pyelogram to define anatomy
- ureteral stent and Foley
- pt placed in 45-degree lateral decubitus position
- 3 laparoscopic ports placed
- identify ureter: for transperitoneal, ureter identified after lateral colon is reflected
- ureter dissected proximally until renal pelvis identified
- ureter and renal pelvis mobilized at UPJ
- renal pelvis transected circumferentially above UPJ
- proximal ureter spatulated laterally
- corner sutures placed w/ 4-0 absorbable
- posterior then anterior anastomosis
- Post-op
  - remove Foley on POD2: replace if drain output increases

### What is the cause of retrocaval ureter?

- persistence of posterior cardinal veins

## **Chapter 13 Questions - Obstruction management.doc**

### **What are the possible etiologies of ureteral stricture?**

- Neoplastic: TCC, cervical
- Metabolic: stones, treatment of stones
- Radiation
- Trauma: ischemia due to surgical dissection, endoscopic instrumentation
- Inflammatory: periureteral fibrosis, AAA, endometriosis
- Infection: TB, schistosomiasis
- Idiopathic

### **What diagnostic studies should be performed to diagnose ureteric stricture?**

- IVP
- retrograde pyelogram
- ureteroscopy w/ barbotage or biopsy → for any pt for whom the etiology of stricture is not certain
- intraluminal US
- diuretic renography

### **What are the indications for intervention for ureteric stricture?**

- to rule out malignancy
- compromised renal function
- recurrent pyelo
- pain associated w/ obstruction

### **What are the options for intervention for ureteric stricture?**

- balloon dilation under fluoro
  - antegrade vs. retrograde
  - direct vision
  - low-profile balloon through ureteroscope
- endoureterotomy
  - antegrade
  - ureteroscopic
  - combined
    - "cut-to-light" procedure
  - cautery wire balloon
- open surgical repair
  - ureteroureterostomy
  - reimplant
  - psoas hitch
  - boari flap
  - transureteroureterostomy
  - renal descensus
  - ileal ureteral substitution → extremely difficult: do not attempt unless have experience
  - intubated ureterotomy
  - autotransplant

### **What are the results for treatment of ureteral stricture?**

- balloon dilation
  - nonanastomotic: 85%
  - anastomotic: 50-75%
- cut-to-light procedures
  - poor success rates w/o permanent stenting, but will improve QOL in some
- ureteroureterostomy
  - > 90% if watertight

### **What are the contraindications to balloon dilation of the ureter?**

- active infection
- long segment of obstruction (>2cm)

### **In which patient population does balloon dilation of the ureter work the best?**

- iatrogenic, nonanastomotic stricture, such as those following instrumentation: 85% success

## **Chapter 13 Questions - Obstruction management.doc**

### **Where is the appropriate position for the incision during endoureterotomy?**

- due to the level of ureter involved
  - lower ureteral strictures: incised in anteromedial direction, away from the iliac vessels
  - mid and upper ureter: incise laterally or posterolaterally, away from the great vessels

### **In what level of ureter should cautery wire balloon incision never be used, and why?**

- in close proximity to great vessels: at iliac level of ureter

### **What length of ureteric defect can be bridged w/ each form of surgical reconstruction?**

- ureteroureterostomy: 2-3 cm → **short defects only**
- ureteroneocystotomy: 4-5 cm
- renal descensus: 5-8 cm
- ureteroneocystotomy + psoas hitch: 6-10 cm
- ureteroneocystotomy + Boari flap: 12-15 cm

### **What are the indications for ureteroureterotomy?**

- **short defects only**
  - short defect in mid-upper ureter
  - congenital anomalies
    - retrocaval ureter
    - duplex system w/ ectopic ureter to upper pole moiety
  - donor ureteral stricture in transplant pt

### **What is the best management option for a lower ureteral stricture?**

- ureteroneocystotomy +/- psoas hitch or Boari flap

### **Describe the procedure of ureteroureterostomy.**

- Preop
  - assess location and length of the stricture
    - only short defects should be managed by u-u
  - IVP and retrograde
  - diuretic renogram
  - ureteroscopy + barbotage
- OR
  - incision
    - flank: upper ureter
    - Gibson: mid ureter
    - Pfannenstiel or lower midline: lower ureter
  - retroperitoneal space is developed
  - peritoneum mobilized and retracted medially
  - identify ureter as it crosses the iliacs
  - place loop around ureter
  - preserve the adventitia
  - excise devitalized tissue: esp w/ gunshot
  - minimize handling of the ureter
  - spatulate for 5-6mm: can transect if dilated
  - place corner sutures
  - run in 2mm bites, or interrupt
  - place stent before finishing
    - reflux of methylene blue from bladder can be used to confirm placement
  - mobilize retroperitoneal fat to surround anastomosis
  - place JP drain
- Postop
  - Foley x 1-2d
  - JP x 1-2d: must differentiate from urine
  - stent x 4-6weeks

### **What incision should be used to access each portion of the ureter?**

- flank: upper ureter
- Gibson: mid ureter



## Chapter 13 Questions - Obstruction management.doc

- Pfannenstiel or lower midline: lower ureter

### What operative maneuvers should be employed while handling the ureter?

- preserve the adventitia
- excise devitalized tissue
- minimize handling of the ureter

### What are the indications for a psoas hitch?

- distal ureteric injury
- ureteral fistula secondary to pelvic surgery
- distal ureteric tumour requiring resection
- failed ureteroneocystotomy

### What are the contraindications for a psoas hitch?

- small contracted bladder
- ureteral defect proximal to the pelvic brim: require more than a psoas hitch alone

### What structures are divided in a psoas hitch to gain additional length?

- divide all peritoneal attachments
- divide vas or round ligament
- contralateral superior vesical artery

### What are the appropriate dimensions of a Boari flap, and how should it be defined?

- posterolateral bladder flap based on ipsilateral superior vesicle artery
- base of flap should be 4cm, tip should be 3cm in width
- **flap length should be as long as the ureteral defect + 3-4cm**

### What are the contraindications to transureteroureterotomy?

- Absolute
  - donor ureter that is too short to reach the contralateral ureter w/o kinking or tension
  - diseased recipient ureter
- Relative
  - urothelial tumour
  - nephrolithiasis
  - radiation
  - chronic pyelo
  - retroperitoneal fibrosis
  - any disease process that involves both ureters
  - previous ureteral surgery or mobilization
  - VUR to recipient ureter

### Describe the technique of TUU.

- midline transperitoneal approach
- peritoneum incised
- colon reflected on side of diseased ureter
- ureter mobilized, preserving adventitia
- contralateral colon reflected, exposing only small amount of normal ureter
- **tunnel under sigmoid colon created → superior to IMA**
- donor ureter brought over to contralateral side
- minimize mobilization of recipient ureter
- **anteromedial** ureterotomy created
- stent from donor renal pelvis through anast into bladder

### What are the contraindications to ileal ureteral substitution?

- elevated creatinine
- bladder dysfunction
- BOO
- IBD
- radiation enteritis

## **Chapter 13 Questions - Obstruction management.doc**

### **What are the potential complications of ileal ureteral substitution?**

- extravasation w/ fistula
- urinoma
- obstruction from edema, mucus plug, kink in the loop
- ischemic necrosis of the loop
- electrolyte abnormalities
- renal insufficiency
- vesicourethral dysfunction

### **What is the incidence of ureteroenteric anastomotic stricture?**

- 4-8% in conduits, more common on L  
→ due to additional length needed, and angulation on IMA increase incidence on L side
- 4-25% in continent diversions → most occur in 1<sup>st</sup> 2 years  
→ increased risk in nonrefluxing anastomosis

### **What are the indications for investigation of ureteroenteric anastomotic stricture?**

- decrease in renal function
- loss of VUR on routine loopogram
- mass at level of the stricture

### **What are the indications for intervention of anastomotic stricture?**

- pain
- infection
- renal insufficiency associated w/ obstruction

### **How can one manage the ureteroenteric anastomotic stricture?**

- dilation alone
- electroincision w/ electrode
- hot wire cutting balloon
- laser incision
- open reimplant

### **Describe the presentation of RPF.**

- middle-aged patient: most common in age 40-60
- anuria
- characteristic back pain: dull, constant, girdle distribution  
→ relieved by aspirin, but not by narcotics
- lower extremity edema, DVT
- constitutional sx: fever, malaise, anorexia, N/V, weight loss, anemia

### **What diseases are associated w/ RPF in kids?**

- JRA, SLE

### **What syndrome is associated w/ RPF in adults?**

- multifocal fibrosclerosis: RPF, sclerosing mediastinitis, sclerosing cholangitis, orbital pseudotumour, Reidel's thyroiditis

### **What are the potential causes for RPF?**

- Drugs: **methysergide** (Sansert), **ergot alkaloids**, hydralazine, reserpine, haldol, LSD, methyl dopa, beta blockers, phenacetin, amphetamines
- Chemicals: avitine, methacrylate, talc
- Malignancy: retroperitoneal tumours → lymphoma (most common), carcinoid, MM, pancreas, prostate, sarcoma
- Inflammatory processes: ascending lymphangitis, IBD
- Hemorrhage: abdo/pelvic surgery, ruptured viscus, HSP w/ hemorrhage
- Periarteritis: AAA, atherosclerosis w/ inflammation, collagen vascular disease
- Infection: gonorrhea, TB, UTI, syphilis, actinomyces, schistosomiasis
- Radiation
- Misc: sarcoid, biliary tract disease, endometriosis

### **What is the potential etiology of RPF?**

- ? immune mediated from Ag response:

## Chapter 13 Questions - Obstruction management.doc

→ ceroid: complex polymer of oxidized lipids and protein found in atherosclerotic plaques

### What is the workup for RPF, and the expected findings?

- Labs: ESR (increased), WBC (increased), Cr (increased), electrolyte abnormalities, anemia
- IVP or retrograde: medial deviation of middle 1/3 of ureter
  - smoothly tapered ureter at level of obstruction
  - lack of filling defect
- CT/MRI: flat confluent retroperitoneal mass enveloping great vessels
- diuretic renogram

### What is the management of RPF?

- Acute
  - decompress kidneys w/ bilateral ureteric stents or NT
    - do retrogrades at this time
  - watch for postobstructive diuresis: replace fluids as needed
  - discontinue all inciting medications
  - biopsy mass: may not be needed if classic features on MR/CT + no peripheral l/a + no hx malignancy
- Medical
  - steroids: if active inflammation on biopsy + increased ESR, WBC
  - other immunosuppressives: azathioprine, MMF, tamoxifen (mechanism unknown)
- Surgical:
  - formal ureterolysis w/ midline incision or laparoscopy, surround ureters w/ omentum
    - used in pts that fail medical therapy or in pts w/ unclear dx at time of bx
    - post-op steroids may prevent recurrence
  - nephrectomy
    - if no renal fn after suitable length of time of decompression, normal contralateral kidney



## **Chapter 14**

### **• Infections of the Urinary Tract •**

---

#### **What are the definitions of the following terms:**

- urinary tract infection = inflammatory response of the urothelium to bacterial invasion
- bacteriuria = presence of bacteria in the urine
- pyuria = presence of WBC in the urine
  - bacteriuria w/o pyuria = colonization
- acute pyelonephritis = F/C w/ back pain + bacteriuria + pyuria → infection of the kidney
- chronic pyelonephritis = shrunken scarred kidney, diagnosed by morphologic, radiologic or functional evidence of renal disease
- cystitis = inflammation of bladder
- urethritis = inflammation of urethra
- uncomplicated infection = infection in healthy pt w/ normal urinary tract
- chronic: poor term, do not use (only for chronic prostatitis)
- complicated infection = infection in pt who is compromised or has urinary tract w/ structural or functional abnormality
  - increased chance of acquiring infection or reduce efficacy of therapy
- recurrent infection = UTI due to reinfection or bacterial persistence
- reinfection = UTI w/ different bacteria from **outside** the urinary tract
- bacterial persistence = recurrent UTI from same bacteria from focus within urinary tract

#### **How can UTIs be classified?**

- isolated infections
  - isolated from previous infections by 6 months
- unresolved infections
  - indicates inadequate initial therapy
- recurrent infections that are reinfections
- recurrent infections from bacterial persistence

#### **What are the causes of unresolved bacteriuria during therapy?**

- bacterial resistance
  - previous vs. development of resistance
  - tetracyclines, sulfa, pen usu resistant via plasmid (R factor)
  - nitrofurantoin and quinolones do not have plasmid-mediated (R factor) resistance
- 2 different bacterial species → unmasks 2<sup>nd</sup> bug
- reinfection w/ new, resistant species during initial tx for original susceptible organism
- azotemia
  - diseased kidney cannot achieve bactericidal concentrations of antibiotic
- papillary necrosis
- staghorn calculi
- Munchausen's syndrome

#### **What urologic abnormalities cause bacterial persistence?**

**(mnemonic: PERSISTAANCC)**

- Prostatitis: chronic bacterial prostatitis
- Ectopic: ureteral duplication and ectopic ureters
- R: foReign bodies
- Sponge: MSK
- Infection stones
- Stumps: nonrefluxing infected ureteral stumps after nephrectomy
- Tics: urethral diverticulae and infected periurethral glands
- Atrophic: unilateral infected atrophic kidneys

## Chapter 14 Questions - UTIs.doc

- Abscess: perivesical abscess w/ bladder fistula
- Necrosis: papillary necrosis
- Cysts: infected urachal cysts
- Calyces: infected communicating cysts of the renal calyces

### What are the RF for developing a UTI?

- female
- increased age
- institutionalization/hospitalization
- concurrent disease
- indwelling catheter
- previous UTI

### What is the incidence of UTI?

- UTI **more common in women** except in neonatal period
  - 1% schoolgirls (5-14 yrs) have bacteriuria – increases to 4% by young adulthood, as well as 1-2% per 10y
  - prevalence in F is 30X that of M
  - w/ increasing age, ratio of F:M w/ bacteriuria progressively decreases
- prevalence **increases w/ institutionalisation**
  - > 80% of nosocomial UTIs are secondary to an indwelling urethral catheter
- pt w/ UTI more likely to develop subsequent UTI
  - probability of recurrent UTI increases w/ number of previous UTI
  - 75% of these reinfections will be different organisms

### What is the natural hx of UTIs?

- 60-80% of women untreated will clear infection
  - 50% of these will be bacteriuric by 1yr (reinfection w/ new or different organism)
- whether pt gets tx or not, risk of recurrent bacteriuria remains same
  - treatment only changes time until recurrence
- prophylactic antimicrobial agents for extended periods ( $\geq 6$  months) may decrease infections during the time of prophylaxis, but the rate of infection returns to the pre-treatment rate after prophylaxis is stopped
- recurrent uncomplicated UTI long-term effects not known
  - in pregnant women, prevalence and rate are same, but progression to acute pyelo more frequent

### What are the routes of infection for UTIs?

- Ascending route
  - most bacteria enter urinary tract from fecal reservoir via ascent through urethra to bladder
    - enhanced if fecal soilage, women using spermicidal agents, and pts w/ CIC or indwelling Foley
  - further ascent into upper tract in 50%
    - edema from cystitis may distort anatomy to allow some reflux
  - ascent enhanced if bacteria have special adhesions
  - G-ve bacteria, endotoxins, pregnancy and ureteral obstruction have antiperistaltic effect
  - once bacteria enter renal pelvis, enter kidney through papilla → increased if VUR or obstruction
- Hematogenous route
  - kidney occasionally infected w/ *S. aureus* bacteremia from oral sites or w/ *Candida*
  - infection enhanced w/ kidney obstructed
- Lymphatic route – rare: bowel infection, retroperitoneal abscess

### What are the etiologic causes of UTIs?

- Urinary pathogens
  - *E. Coli* is most common cause of UTI → 85% community-acquired, 50% hospital-acquired
    - the rest caused by: *Proteus*, *Klebsiella*, *enterococcus*, *S. saprophyticus*
    - if DM: usually get *Klebsiella*, group B strep, *Aerococcus*, non-*albicans Candida*
  - *S. saprophyticus* causes UTI in 10% young sexually active women, rare in men/elderly
- Fastidious Organisms
  - Anaerobes: rare
    - distal urethra, vag, perineum colonized normally by anaerobes
    - found in suppurative infections in GU tract
    - usual suspects: *Bacteroides*, *Fusobacterium*, *Clostridium*
  - *Mycobacterium Tuberculosis* and other Atypical Mycobacterium

## Chapter 14 Questions - UTIs.doc

- AFB may be seen in sterile pyuria
- Chlamydia

### What bacterial virulence factors exist that can increase chance of UTI?

- **bacteria are selected from fecal flora by presence of virulence factors**
  - allows them to adhere to and colonize the perineum and urethra, and migrate to the GU tract
- hemolysin and cytotoxic necrosis factor, the siderophore aerobactin, capsules, lipopolysaccharide (LPS), adhesive organelles
  - hemolysis in *E. coli* causes pyelo in rats
  - serological O group *E. coli* (more likely to produce hemolysin)
- K antigen = capsular acidic polysaccharide
  - cause pyelonephritis
- adhesive organelles: P pili, type 1 pili

### What factors affect bacterial adherence and colonization?

- virulence factors
  - hemolysin, CNF, LPS
- bacterial adhesins: cell structures that allow bacteria to bind to epithelial cells
  - P pili, type 1 pili
- phase variation of pili
  - environmental growth conditions can produce rapid changes in pilus expression – change back and forth from pili to no pili
    - pili enhance phagocytosis and destruction by neutrophils
- epithelial cell receptivity
  - *E. coli* strains that cause cystitis adhere more to epithelial cells from susceptible women
  - A3 antigen may be associated w/ increased risk of recurrent UTI
  - relationship between vaginal cell and buccal cell receptivity
  - blood group antigens are important part of the uroepithelial cell membrane
    - women with Lewis blood group Le(a-b-) and Le(a+b-) (nonsecretor) phenotypes have higher incidence of recurrent UTIs than women with Le(a-b+) phenotype
- variation of cell receptivity
  - variation in vaginal and buccal cell receptivity from day to day
  - premenopausal women susceptible at certain times during the menstrual cycle and early pregnancy
  - uropathogens attached in larger numbers to uroepithelial cells from women > 65 years
    - increased colonization by *E. coli*
- primary bladder and vaginal defenses
- intercourse, antibiotics, intravaginal antibiotics: reduce normal lactobacillus and increase susceptibility to UTI

### What are bacterial adhesins?

- long, filamentous protein appendages called *pili* or *fimbriae* - composed of subunits known as *pilin*
  - cell structures that allow bacteria to bind to epithelial cells
- defined by their ability to mediate hemagglutination (HA) of specific types of erythrocytes
  - Mannose-Sensitive (Type 1) Pili
    - mediate HA of guinea pig erythrocytes → mediated by the addition of mannose
    - Fim H, the adhesin on the tip of type 1 pili very important
    - uroplakins (bladder cell surface protein), UPIa and UPIb, bind *E. coli* expressing type 1 pili by Fim H
  - Mannose-Resistant (P) Pili → related to Type 1 Pili
    - bind  $\alpha$ -d-galactopyranosyl-(1-4)- $\beta$ -d-galactopyranoside moiety in glycolipids
    - mediate HA of human erythrocytes – not mediated by addition of mannose (MRHA)
    - **P pili present in most bacteria causing pyelo**, few bacteria causing cystitis or asymptomatic bacteriuria
    - recurrent pyelo with gross reflux minimally associated with P-piliated *E. coli* strains
      - ◆ P pili in acute pyelonephritis important mainly in nonrefluxing or minimally refluxing children

### What are the primary bladder and vaginal defenses against UTI?

- **flow of urine and voiding → #1 defense**
  - low pH and osmolarity of urine: inhibitory to bacterial growth
  - salts, urea, organic acids in urine: reduce bacterial survival
  - lactoferrin within urine: can scavenge essential iron away from bacteria
  - sugars and IgA: antiadherence factors
  - antibacterial effects of bladder mucosa

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- urinary and local antibodies
- PMNs
- cytokines
- vaginal flora
  - sex, antibiotics, intravaginal antimicrobials, spermicides → reduce lactobacillus-dominant vaginal flora and increase susceptibility to UTI
- mucopolysaccharides that coat the bladder wall
  - uromucoid: *E. coli* strains w/ type 1 pili trapped in vitro by uromucoid (Tamm-Horsfall protein) and thus blocked from attaching to uroepithelial cells
- vaginal mucus and secretory IgA

### How can one collect urine for dx of UTI?

- SP aspiration
  - doesn't introduce urethral bacteria
  - 20-ml syringe to aspirate 5 ml of urine for culture and 15 ml of urine for centrifugation and urinalysis
- CIC (female only)
  - some specimens contaminated regardless of technique
  - > 100 or more CFUs / mL of a uropathogen indicates infection
  - easiest way to prevent catheter-induced infections is to give 1-2 tabs abx (ex: Septra) → decreases 35% to 4% bacteriuria
    - antibacterial solutions also can be left in the bladder after catheterisation
- segmented voided specimens
  - women: spread labia; wipe periurethral area with clean sponge, collect specimen while separate labia
    - no antiseptic: may contaminate the specimen and cause false-negative
  - male: urethral and bladder urine specimens (separated) as reliable as SP aspiration

### How high must the bacterial count be before bacteria seen during U/A?

- bacterial count must be approximately 30,000/ml before bacteria can be found in the sediment
  - -ve U/A never excludes the presence of bacteria in numbers of < 30000/ml
  - can have false +ve UA: lactobacilli and corynebacteria readily seen under microscope
    - are gram-positive, but appear gram-negative (gram-variable) if stained
- validation of the MSU can be questioned if squamous epithelial cells (indicative of preputial, vaginal, or urethral contaminants) are present

### What are the indicators of UTI on urinalysis?

- pyuria and hematuria: good indicators
  - hematuria very specific, 40%-60% sensitive
  - WBC quantitated by WBC excretion rate (in a timed urine collection) as WBCs per hour or the WBC concentration as WBCs per millilitre
    - women without evidence of urinary tract disease excrete fewer than 400,000 leukocytes/hr
    - pyuria = >10 WBCs/mm<sup>3</sup> of urine
    - absence of pyuria should cause the diagnosis of UTI to be questioned
- nitrites: formed when bacteria reduce the nitrate present in urine
- leukocyte esterase activity: sensitivity of 75% to 96% in detecting pyuria associated with infection
  - false-positive results are relatively uncommon, but borderline sensitivity → microscopy more sensitive

### What is the Ddx of pyuria with a negative culture?

- GU TB, staghorn calculi and other stones
- any injury to GU tract: urethritis, GN, IC

### What mediums are used to culture urine?

- direct surface plating of 0.1 mL urine on split-agar
  - blood agar - grows both gram-positive and gram-negative bacteria
  - desoxycholate or eosin-methylene blue (EMB), which grows gram-negative bacteria
- dip-slides w/ soy agar (a general nutrient agar to grow all bacteria) on one side and EMB or MacConkey's agar on other
  - 1/100 - 1/200 mL urine attaches, so multiply by 100-200 to get CFU
- urine must be refrigerated immediately on collection and should be cultured within 24 hours of refrigeration

### What is the cutoff for significant bacteriuria?

- 20% to 40% of women with symptomatic UTIs have bacteria counts of 10<sup>2</sup> to 10<sup>4</sup> cfu/ml of urine

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- slow doubling time of bacteria in urine (every 30 to 45 minutes) combined with frequent bladder emptying (every 15 to 30 minutes) from irritation
- in dysuric patients, significant bacteriuria is  $10^2$  cfu/ml of a known pathogen
- $10^5$  CFU/mL cutoff → overdiagnosis

### How may one localize a UTI to the kidney?

- Sx: fever and flank pain
  - thought to indicate pyelonephritis, but may be localized to the bladder
- Ureteral Catheterization
  - allows separation of bacterial persistence into upper and lower urinary tracts, L vs. R kidney
    - bladder must be thoroughly irrigated
    - sample is obtained through both ureteral catheters simultaneously
    - 4 serial cultures from each kidney
- Fairley Bladder Washout Test
  - washing bladder free of bacteria then collect serial cultures representing upper tract urine
  - useful technique in studies of recurrent UTIs in pts w/o significant abnormalities of the GU tract
  - *bladder is emptied through a urethral catheter and 40 ml of 0.2% neomycin instilled w/ "Erase" (fibrinolysin and deoxyribonuclease)*
  - *After 10 minutes, bladder distended with 0.2% neomycin to reduce folds in the mucosa*
  - *bladder emptied and washed out with 2 L of NS*
  - *final washout is collected for culture, then three timed specimens collected at 10-minute intervals*
    - Renal infection = timed specimen 20 to 30min after bladder washout has > 3000 bacteria/ml
    - Bladder infection = final timed specimen (20 to 30 minutes after the bladder washout) sterile
- Immunologic Responses
  - Direct Agglutination Tests
    - mixing dilutions of serum with bacterial suspensions
    - presence of IgM Ab against bacteria detected by agglutination of particles
    - limited use in detecting chronic infections, in which IgG is more important
  - Passive Agglutination Tests
    - bacterial polysaccharide and protein Ag may stick nonspecifically to RBC
    - mixed with dilutions of serum → agglutination of RBC
  - Antibody-coated Bacteria
    - fluorescein-conjugated anti-human globulin mixed w/ bacteria in urine
      - ◆ pyelonephritis → bacteria fluorescent antibody-positive (FA<sup>+</sup>)
      - ◆ cystitis → bacteria not antibody-coated (FA<sup>-</sup>)
    - false-positive findings caused by local production of bladder Ab have invalidated test in children
  - Enzyme-linked Immunosorbent Assay (ELISA) and Radioimmunoassays for Immunoglobulins (RIA)
    - labeled antisera to Ig heavy-chain fractions of IgM, IgG, and IgA to detect Ab to bacteria (Ag-specific Ab)
    - more sensitive and quantitative than agglutination or HA tests

### What is the Ig response in pyelonephritis?

- acute pyelonephritis → Ab to infecting bacteria can be measured in serum
- bacterial agglutination studies: IgM against bacteria elevated in acute pyelo
  - titers decreased after pyelo treated but persistently elevated when pt remained infected
- IgA and SIgA also appear in the urine → synthesized locally
- antibodies more elevated in pyelo than in cystitis
- serum antibody is not the result of antibody synthesized in the kidney

### What is the diagnostic utility of antibody titers?

- cannot diagnose pyelo vs. cystitis by using Ab titers or fluorescent Ab-coated bacteria tests
- may be more useful in chronic bacterial infections

### How can one localize a UTI to a stone?

- stone put in 5cc NS
- agitation of stone x4 w/ culture of 0.1mL
- stone is crushed in 4<sup>th</sup> saline wash
- difference b/w fourth saline wash before and after crushing is difference b/w surface bacteria and bacteria within the specimen

### What are the indications for radiologic investigations in acute clinical pyelonephritis?



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### (mnemonic - RADIOLOGICCK)

- Response: Poor response to appropriate antimicrobial agents after 5–6 days of treatment
  - r/o perinephric or renal abscesses
- Analgesic abuse: Papillary necrosis (e.g., patients with sickle cell anemia, severe diabetes mellitus, analgesic abuse)
- DM: may get emphysematous pyelo or papillary necrosis
- Infections: Unusual infecting organisms, such as tuberculosis, fungus, or urea-splitting organisms (e.g., *Proteus*)
  - look for abnormalities within the urinary tract, such as strictures, fungus balls, or obstructing stones
- Obstruction: potential ureteral obstruction (e.g., due to stone, ureteral stricture, tumor)
  - pt may require intervention + abx
- L
- OR: hx GU surgery that predisposes to obstruction, (ex: ureteral reimplantation or ureteral diversion)
- Genic: neurogenic bladder
- I
- Calculi: history of calculi, especially infection (struvite) stones
- Cystic kidneys: PCKD in patients on dialysis or with severe renal insufficiency

### What imaging techniques can be used in UTIs?

- KUB
  - radiopaque calculi and unusual gas patterns in emphysematous pyelonephritis
  - absent psoas or abnormal renal contour
- Plain Film Renal Tomograms
  - small or poorly calcified stones despite overlying gas
  - struvite and uric acid stones that contain small amounts of calcium may be seen
- IVP
  - useful to determine the exact site and extent of urinary tract obstruction
  - not the best screening test for hydronephrosis, pyonephrosis, or renal abscess
    - unnecessary for routine evaluation
- VCUG
- Renal US
  - useful in r/o hydronephrosis associated with UTI, pyonephrosis, and perirenal abscesses
  - no radiation or contrast agent risk
- CT and MR
  - best anatomic detail
  - more sensitive than IVP or U/S for acute focal bacterial nephritis and renal and perirenal abscesses
- MR: advantages in delineating extrarenal extension of inflammation
- Radionuclide Studies
  - Gallium-67
    - used to distinguish some upper tract from lower tract infections
    - possible mechanisms:
      - ◆ concentration within labeled PMNs
      - ◆ leakage of protein-bound gallium through capillaries
      - ◆ increased vascularity of the lesion
    - can see focal bacterial nephritis and infected renal cysts
    - disadvantage: unable to differentiate simple inflammatory processes from pyelonephritis, pyonephrosis, perirenal abscess, or renal tumors
  - Indium-111
    - Indium 111-labeled WBC accumulate only in sites of inflammation and not in normal kidneys or tumors
    - highly specific for inflammation
    - disadvantages
      - ◆ hyperalimentation and hyperglycemia can prevent accumulation at site of inflammation
      - ◆ distribution of WBC altered in patients who have had splenectomy or bone marrow radiation
  - useful if
    - cases in which intra-abdominal **abscess suspected but localizing signs are absent**
    - cases in which clinical suspicion of abscess remains high but U/S and CT **studies equivocal** or negative

### What are the indications for IVP in UTIs?

- neuropathic bladders
- female patient who has a urethral diverticulum causing her persistent infections

### How can one classify bacterial resistance to antibiotics?

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- “natural” resistance
  - absence of drug-susceptible substrate in some species (ex: *Proteus* always R to Macrobid)
- selection of resistant mutants within the urinary tract during therapy
  - resistant organism (clone) was present before, but only in one per  $10^5$  to  $10^{10}$  organisms
  - occurs 5-10% of the time
- transferable, extra-chromosomal, plasmid-mediated (R factor) resistance
  - much more common
  - produces multiply resistant strains, making therapy more difficult
  - occurs only in the fecal flora, never within the urinary tract

### What factors modify drug resistance?

- influenced by the amount and duration of drug used
- fluoroquinolone resistance of *E. coli* has increased from less than 1% to 7% in hospitalized patients

### What are the mechanisms of action and drug resistance for the following drug classes:

- $\beta$ -Lactams (penicillins, cephalosporins, aztreonam): inhibition of bacterial cell wall synthesis
  - Production of  $\beta$ -lactamase
  - Alteration in binding site of penicillin-binding prot
  - Changes in cell wall porin size (dec penetration)
- Aminoglycosides: inhibition of ribosomal protein synthesis
  - Down-regulation of drug uptake into bacteria
  - Bacterial prodx of aminoglycoside-modifying enzyme
- Quinolones: inhibits bacterial DNA gyrase
  - Mutation in DNA gyrase-binding site
  - Changes in cell wall porin size (decreased penetrx)
  - Active efflux
- Nitrofurantoin: Inhibition of several bacterial enzyme systems
  - mechanism of resistance not known — develops slowly with prolonged exposure
    - rapidly excreted in urine, but does not attain therapeutic levels in most body tissues
- Trimethoprim-sulfamethoxazole: Antagonism of bacterial folate metabolism
  - draws folate from environment (enterococci)
    - SMX contributes to efficacy via synergistic bactericidal effect
    - minimal adverse effects on fecal flora
- Vancomycin: acts via inhibition of bacterial cell wall synthesis (at different point than  $\beta$ -lactams)
  - enzymatic alteration of peptidoglycan target

### What bacteria are covered by the following antibiotics:

- Amoxicillin or ampicillin
  - *Streptococcus*, Enterococci
  - *Escherichia coli*, *Proteus mirabilis*
- Amoxicillin with clavulanate: increased activity against  $\beta$ -lactamase producing bacteria
  - *Streptococcus*
  - *E. coli*
- Ampicillin with sulbactam
  - *Staphylococcus* (not MRSA), Enterococci
  - *P. mirabilis*, *Haemophilus influenzae*, *Klebsiella* species
- Antistaphylococcal penicillins
  - *Streptococcus*, MSSA
  - No gram -ve
- Antipseudomonal penicillins
  - *Streptococcus*, Enterococci
  - Most gram -ve, including *Pseudomonas*
- First-generation cephalosporins → no enterococcus
  - *Streptococcus*, MSSA
  - *E. coli*, *P. mirabilis*, *Klebsiella*
- Second-generation cephalosporins (cefamandole, cefuroxime, cefaclor) → no enterococcus
  - *Streptococcus*, *Staphylococcus* (not MRSA)
  - *E. coli*, *P. mirabilis*, *H. influenzae*, *Klebsiella* species
- Second-generation cephalosporins (cefoxitin, cefotetan) → no enterococcus
  - *Streptococcus*

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- *E. coli*, *Proteus* species (including indole +), *H. influenzae*, *Klebsiella*
- Third-generation cephalosporins → no enterococcus
  - *Streptococcus*
  - Most gram -ve, including *P. aeruginosa*
- Aztreonam
  - No gram +ve
  - Most gram -ve, including *P. aeruginosa*
- Aminoglycosides
  - *Staphylococcus* (urine)
  - Most gram -ve, including *P. aeruginosa*
- Fluoroquinolones
  - *Streptococcus*
  - Most gram -ve, including *P. aeruginosa*
- Nitrofurantoin
  - *Staphylococcus* (not MRSA), Enterococci
  - Many Enterobacteriaceae, *Klebsiella* species: **not good against *Pseudomonas*, *Proteus*, upper tract infections**
- Trimethoprim-sulfamethoxazole
  - *Streptococcus*, *Staphylococcus*
  - Most Enterobacteriaceae (not *P. aeruginosa*)
- Vancomycin
  - All gram +ve, including MRSA
  - No gram -ve

### What are the common adverse reactions seen with the following antibiotics:

- Amoxicillin or ampicillin: hypersensitivity, diarrhea (esp. with ampicillin), GI upset, pseudomembranous colitis, maculopapular rash (not hypersensitivity), decreased platelet aggregation
  - increased risk of rash with concomitant viral disease, allopurinol therapy
- Amp with sulbactam: diarrhea, GI upset with amoxicillin/clavulanic acid
- Antistaph penicillins: Same as with amoxicillin/ampicillin, GI upset (with oral agents), AIN (esp. methicillin)
- Antipseudomonal penicillins: Same as with amoxicillin/ampicillin, hyponatremia (these drugs are given as sodium salt; esp. carbenicillin, ticarcillin), local injection site reactions
  - use with caution in patients very sensitive to sodium loading
- Cephalosporins: hypersensitivity (less than with penicillins), GI upset (with oral agents), local injection site reactions, pseudomembranous colitis, positive Coombs' test, decreased platelet aggregation
  - don't use if immediate hypersensitivity to penicillins
  - may use with caution in patients with delayed hypersensitivity reactions
- Aztreonam: hypersensitivity (less than with penicillins)
  - less than 1% incidence of cross reactivity in penicillin/ceph
- Aminoglycosides: ototoxicity—vestibular and auditory components, nephrotoxicity—nonoliguric azotemia, neuromuscular blockade with high levels
  - avoid in pregnant patients, impaired renal function, diabetes, or hepatic failure
  - use with caution in myasthenia gravis (potential for neuromuscular blockade)
- Fluoroquinolones: Mild GI effects; dizziness, lightheadedness; photosensitivity, CNS effects, including dizziness, tremors, confusion, mood disorder, hallucinations, tendon rupture
  - arthopathic effects if kid/pregnant
  - concomitant antacid (w/ Mg or Al) or iron or zinc or sucralfate use dramatically decreases oral absorption
  - can increase theophylline plasma levels
  - can lower seizure threshold
  - can enhance warfarin effects—closely monitor coagulation tests
- Nitrofurantoin: GI upset, peripheral polyneuropathy, hemolysis in patients with G6PD deficiency, pulmonary hypersensitivity reactions
  - monitor long-term patients closely
  - avoid concomitant magnesium or quinolones, which are antagonistic to nitrofurantoin
- Trimethoprim-sulfamethoxazole: hypersensitivity, **rash, GI upset**, photosensitivity, hematologic toxicity (AIDS patients)
  - avoid in pregnant patients, patients receiving warfarin
  - increased risk of hematologic effects in folate- or G6PD-deficient patients
  - ensure adequate hydration to avoid crystallization of drug in urinary tract
- Vancomycin: “Red-man’s syndrome”—flushing, fever, chills, rash, hypotension (histaminic effect), nephrotoxicity and/or ototoxicity, local injection site reactions

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- use with caution with other potentially ototoxic and nephrotoxic drugs

### What factors affect choice of antibiotic for UTIs?

- complicated or uncomplicated
- spectrum of activity of the drug against the probable pathogen
- history of hypersensitivity
- potential side effects, including renal and hepatic toxicity
- cost

### What is the optimal duration of therapy for the following UTIs?

- Symptomatic Acute Cystitis
  - 3-day therapy optimal → no difference in cure rates, side effects are reduced, and cost decreased
  - 7-day regimen → if symptoms for over 7 days, recent UTI, older than 65 years, DM, or pregnancy
  - single-dose therapy → resolution of symptoms slower and the failure / recurrence rates greater
  - in men:
    - 7-day course of TMP-SMX, TMP, or a fluoroquinolone
    - referred for urologic evaluation if recurrent
    - In older men, all UTIs should be treated as if they are complicated
- Acute Uncomplicated Pyelonephritis in Women
  - outpatient infection without sepsis, N/V, not pregnant: PO 7-14d fluoroquinolone (better than Septra)
  - outpatient infection w/ sepsis or need admit: IV quinolone, AG, 3<sup>rd</sup> generation cephalosporin
    - if gram +ve: amoxicillin or amoxicillin-clavulanic acid
    - convert to PO x 2/52 when stable
  - pregnant: ceftriaxone 1-2g IV q24h or aztreonam 1g IV q12h x 14d until afeb, then Keflex x 14d
- Patients with Unresolved or Complicated Infections
  - 14-21d therapy:
    - if remain bacteriuric on antimicrobial therapy
    - have structural or functional abnormalities of the urinary tract
    - abnormal host defenses
  - moderately ill, no N/V, and can be treated as an outpatient → fluoroquinolone 1<sup>st</sup> line
    - Cipro 500mg PO q12h, Levofloxacin 500mg PO OD, Norfloxacin 400mg PO q12h
  - severe infection → broad-spectrum IV then PO
    - IV amp/gent, IV cipro, ceftriaxone, then PO quinolone

### What are the indications for antimicrobial prophylaxis for transurethral procedures?

- UTI present: treat pre-procedure
  - if bacteria present, 50% become bacteremic
- risk of SBE: valvular disease, replacement valve
  - for transurethral GU procedures, including catheterizx, catheter manipulation, cysto, and urethral dilatx
  - Amp 2 g + gent 1.5mg/kg IV (not to exceed 80 mg), then amoxicillin 1.5g PO 6 hours later
  - Pen allergic: Vanco 1g IV over 1 hour + gent 1.5 mg/kg IM/IV 1 hour before, repeat 8h later
- indwelling catheter = infected
  - need at least two doses of a drug that has broad coverage against G-ve's (ex: AG)
  - quinolone or Septra started day before the catheter removed, continue for 3 to 5 days after
- TURP/transurethral procedures: need for antibiotics in TURP/transurethral procedures is controversial
  - postoperative UTIs decrease when antibiotics used
  - if no growth (<100 bact/mL) in preop urine and no G-ve organisms in urethra, probably no prophylaxis needed
    - **if not known, 6-12% have unsuspected bacteriuria w/ a 50% chance of becoming bacteremic**

### What are the AUA Guidelines for antibiotic prophylaxis for urologic pts w/ total joint replacements?

- antibiotic prophylaxis not indicated for healthy pts w/ orthopedic surgery w/ pins, plates, or screws, or most healthy GU pts w/ total joint replacements
- urine should be sterile prior to procedures
- if orthopod recommendations differ from AUA guidelines, determine the special considerations that may have affected the decision
- consider antibiotics in high risk pts:
  - all pts w/i 2 yrs post-joint replacement
  - **immunocompromised pts**
  - pts w/ **co-morbidities**: previous prosthetic infections, malnourishment, hemophilia, HIV, DM, malignancy
- consider in high risk procedures:

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- stone manipulation (includes ESWL)
- any procedure w/ transmural incision into GU tract (does not include ligation w/ excision or perc drainage procedures)
- ureteroscopy or renoscopy
- TRUS/bx of prostate
- any procedure in pts w/ higher risk of bacterial colonization:
  - indwelling catheter/stent
  - CIC
  - retention
  - hx recent or recurrent UTI or prostatitis
  - diversion
- low risk procedures: prophylaxis not needed
  - urethroscopy/cystoscopy w/o stone manipulation or incision (includes fulgurization and bladder biopsy, if no incision)
  - open surgical/lap procedures w/o stone manipulation or incision into GU tract
  - catheterization for drainage/diagnostic purposes: retrograde or perc
- suggested antibiotics
  - single dose of quinolone: Cipro 500mg, Levaquin 500mg, ofloxacin 400mg PO 1h preop
  - amp 2g IV (or vanco 1-2g over 1h) + gent 1.5mg/kg 30-60mg preop

### What are the complications of TRUS and Bx?

- cystitis, prostatitis, epididymitis, pyelonephritis, local abscess, osteomyelitis, and sepsis
  - 76% of patients after bx are bacteremic (50% w/ anaerobes)
  - enemas with povidone-iodine do not alter the infectious complications
  - quinolone given before the procedure and continued for 1d after is effective

### What are the indications for treatment of asymptomatic bacteriuria?

- infection from *Proteus* species causes struvite stones if left untreated
- severe diabetes
- pregnant women

### What factors place patients at risk of serious morbidity or renal scarring with UTIs?

- obstruction
- urea-splitting bacteria (*Proteus*): cause struvite renal stones
  - causes intense alkalization of the urine with precipitation of Ca, Mg,  $\text{NH}_4^+$ , and  $\text{PO}_4^{3-}$
  - bacteria persist inside these struvite stones even when the urine shows no growth
  - if ESWL used for infection stones, keep on antibiotics until fragments pass
  - if OR, all the residual particles of struvite stones must be removed
    - if fragments remain, irrigation with Renacidin or Suby G solution through NT
  - F/U for *Proteus* stones: need tomograms or U/S as minimal Ca in stone
- congenital urinary tract anomalies
  - duplications, pericalyceal diverticula, urachal cysts of the dome of the bladder, unilateral MSK
- catheter drainage
  - incidence of UTIs in pts with indwelling catheters is directly related to the durx of catheterization
    - incidence of acquired bacteriuria to be about 5% per day of catheterization
- renal papillary necrosis
  - spectrum of disease: acute fulminant illness to chronic
    - diagnosis may be made from the passage of necrotic papillae in the urine
  - X-ray: medullary / papillary changes causing irregular sinuses/cavities or classic ring shadows
  - **analgesic abuse-associated RPN = increased incidence of urothelial tumors → do cytology**
- DM, especially with emphysematous pyelonephritis
  - incidence in DM women 11.4% to 15.8%, compared to 4.5% to 4.6% in controls
  - often have a glomerulopathy, with difficulty concentrating antimicrobial agents
  - predisposed to special complications of UTIs: RPN and emphysematous pyelonephritis
- spinal cord injury with high-pressure bladders
- pregnancy
- acute bacterial prostatitis

### What are the sources of catheter associated UTI?

- periurethral and perineal organism (27%)

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- organisms colonizing the collecting bag or collecting device (45%)
  - breaks in the drainage system caused by opening the closed system for irrigation
  - *E. coli* #1, also *Candida*, *Enterococci*, *Pseudomonas*, *Klebsiella*, *Enterobacter*, and *S. aureus*

### What conditions are associated with renal papillary necrosis?

- Mnemonic - ADIPOSE**
  - Analgesic abuse
  - DM
  - Infantile shock: Dehydration, hypoxia, and jaundice of infants
  - Pyelonephritis
  - Obstruction
  - Sickle-cell hemoglobinopathies
  - Ethanol abuse: Cirrhosis of the liver
  - Renal transplant rejection
  - Miscellaneous: renal vein thrombosis, cryoglobulinemia, renal candidiasis, contrast media injection, amyloidosis, calyceal arteritis, necrotizing angitis, RPGN, hypotensive shock, acute pancreatitis
- Mnemonic - POST CARD:**
- Pyelo, Obstx, Sickle Cell, TB/Transplant, Cirrhosis, Analgesic nephropathy, RVT, DM, Dehydration

### How should one treat UTIs associated w/ an indwelling catheter?

- don't treat bacteriuria/funguria/pyuria as long as catheter remains and pt asymptomatic
- if a urea-splitting bacteriuria identified, treat x 3-5d
- if fever and flank pain, treat for pyelo, r/o obstruction
- if long term catheter, give abx 1d prior to each change

### What is the clinical presentation of acute pyelonephritis?

- Clinical
  - spectrum ranges from gram-negative sepsis to cystitis with mild flank pain
  - classic presentation: abrupt onset F/C, uni- or bilateral CVAT w/ dysuria, frequency, urgency
    - fever and flank pain are no more diagnostic of pyelonephritis than they are of cystitis
- Lab findings
  - 20% of patients have urine cultures with fewer than  $10^5$  cfu/ml
  - urine usually shows increased WBCs, WBC casts, and RBC
  - serum: increased WBC, ESR, C-reactive protein, creatinine (if ARF), + ve blood culture

### What is the etiologic agent in acute pyelonephritis?

- E. Coli* in 80%, esp if *P. pili* present → K antigens and endotoxins also may contribute

### What are the radiologic findings usually found in acute pyelonephritis?

- IVP: renal enlargement during the acute infection in 20%
  - overall length of 15 cm or 1.5 cm > unaffected side = acute pyelonephritis
  - focal bacterial nephritis or acute lobar nephronia looks like mass
  - obstruction of tubules from edema → delayed contrast excretion
  - may see cortical striations in nephrogram phase, dilatation of the ureter and pelvis by the bacterial endotoxins that impair ureteral peristalsis, renal pelvic/ureteral streaks from mucosal edema.
- Renal US: no findings are seen on U/S that are not seen on the urogram
- CT: not indicated unless not dx on urogram or pt doesn't respond after 72h treatment
- angio: unnecessary in acute bacterial pyelonephritis
  - may show attenuated/stretched interlobar arterial branches as well as cortical striations

### What are the pathologic findings in acute pyelonephritis?

- Gross: enlarged, with small yellow-white cortical abscesses mixed with parenchymal hyperemia
- Micro: parenchyma shows patchy focal PMN infiltrate
  - linear bands of inflammation extend from the papillae to cortex later in wedge shaped manner

### What is the treatment of acute pyelonephritis?

- uncomplicated infection that doesn't warrant hospitalization
  - PO quinolones (or amoxicillin or amoxicillin-clavulanic acid if suspect G+ve)
  - 7d for a fluoroquinolone or 14d for TMP-SMX
- uncomplicated infection in pts with N urinary tracts who require hospitalisation and IV abx

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- quinolone or AG +/- ampicillin, or cephalosporin +/- AG
- complicated infection assoc. w/ hospitalization, catheterizx, GU surgery, or GU tract abnormalities
  - aggressive broad spectrum therapy
  - complicated pyelo for 7d w/ IV (2-3d if blood cultures -ve), then PO x 7-14d
- if symptoms persist > 72 hours look for perinephric or intrarenal abscess with CT or US
  - repeat urine and blood cultures at appropriate intervals
  - repeat urine C&S 5-7d after starting antibiotic and 4-6 weeks after stopping
  - 10%-30% with acute pyelo relapse after 14-day course → give 2 more weeks, up to 6 if necessary

### What is the definition of chronic pyelonephritis?

- small, contracted, atrophic kidney or coarsely scarred kidney produced by bacterial infection, whether recent or remote

### What is the cause of scarring associated w/ chronic pyelonephritis?

- Immunologic Response
  - infx stimulates humoral (IgM, IgA, and IgG) and cellular immune responses
  - cause of scarring unclear: WBC response is at least partially responsible
  - bactericidal activity of the neutrophils causes the initial damage to the renal tubular cells
- Reflux Neuropathy
  - renal scarring occurs only in kidneys exposed to reflux with infected urine
  - reflux nephropathy is present in 0.6% to 1% of bacteriuric women
  - nonrefluxing papilla: conical and has papillary ducts that close w/ retrograde calyceal pressure
  - refluxing papilla: at poles of kidney, are larger and have papillary ducts that are wide open

### What is the clinical presentation of chronic pyelonephritis?

- Clinical
  - often no urologic symptoms, and the condition is discovered incidentally
  - pregnant women: may present w/ UTI or renal failure
- Laboratory Findings
  - urine: leukocytes, proteinuria, leukocyte casts (rare)
  - increased creatinine, decreased CrCl

### What are the radiologic findings seen w/ chronic pyelonephritis?

- IVP
  - best technique for diagnosing chronic pyelonephritis
  - kidneys small and atrophic
  - focal coarse renal scarring w/ clubbing of the underlying calyx
- VCUG
  - useful in kids to show VUR (may be assoc. w/ renal scarring)

### What pathologic findings are seen in chronic pyelonephritis?

- Gross: diffusely contracted, scarred and pitted
  - scars are U-shaped, flat, broad-based depressions with red-brown granular bases → at poles
- Histology: nonspecific changes → patchy interstitial infiltrate of WBC, plasma cells, and occasional PMNs
  - some parenchyma replaced w/ fibrosis
  - WBC/hyalin casts occ. w/ tubules → looks like thyroid colloid (*renal thyroidization*)

### What are the clinical sequelae of chronic pyelonephritis?

- acute pyelonephritis does not cause scarring in most adults with normal urinary tracts
- most changes in chronic pyelo occur in infancy (growing kidney susceptible)
- 5-year survival rate of 95%, 10-year survival rate of 86% w/ documented bilat radiologic changes
  - if unilateral, 100% 10 yr survival

### What is emphysematous pyelonephritis?

- acute necrotizing parenchymal and perirenal infection caused by gas-forming uropathogens
  - **mortality of 43%**
  - occurs in diabetic patients: ? high glucose levels converted to CO<sub>2</sub> by fermentation by *E. Coli*
  - many patients have GU tract obstruction with stones or RPN and significant renal functional impairment
  - Organisms: ***E. Coli* is most frequently identified**; *Klebsiella* and *Proteus* are less common
- Type 1: complete renal destruction, Type 2: segmental renal destruction

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### What is the clinical presentation of emphysematous pyelonephritis?

- only in adults, women > men
- severe acute pyelonephritis that fails to resolve within first 3 days of treatment
- classic triad in almost all pts: fever, vomiting, flank pain
  - pneumaturia if collecting system involved

### What are the radiologic findings in emphysematous pyelonephritis?

- hallmark is intraparenchymal gas (mottled gas shadows over the involved kidney) – looks like bowel
  - extends to the perinephric space and retroperitoneum as progresses
- IVP: useless, as kidney usually poorly functioning
- retrograde pyelography or ultrasonography best to dx obstruction
- U/S: strong focal echoes, suggesting the presence of intraparenchymal gas
- CT: localizes the gas and extent of infection
  - with presence of streaky/mottled gas and absence of fluid +/- bubbly/loculated gas on CT = rapid destruction of renal parenchyma and a 50% to 60% mortality rate
  - bubbly/loculated gas + no streaky/mottled gas = more favorable prognosis
- renal scan: to assess renal function in the involved and contralateral kidney

### What is the treatment of emphysematous pyelonephritis?

- start on appropriate antimicrobial agents, treat diabetes, and give rapid supportive measures
- relieve obstruction
- establish function of contralateral kidney (~10 % of reported cases are bilateral)
- selected cases: percutaneous drainage with medical therapy
- surgical drainage or nephrectomy if persistent intraparenchymal renal gas (ineffective treatment)

### What is a renal abscess?

- carbuncle → collection of purulent material confined to the renal parenchyma

### What is the cause of renal abscess?

- in past, > 80% due to hematogenous seeding by staphylococcus
- usually due to **G-ve organisms** → **ascending infection** with tubular obstruction from prior infections or calculi
- 2/3 G-ve abscesses associated with renal calculi or damaged kidneys

### What are the findings associated w/ renal abscess?

- Clinical
  - F/C, abdominal or flank pain, weight loss and malaise, sx of cystitis
  - gram-positive source of infection 1 to 8 weeks before: skin carbuncles and IV drug abuse
  - RF: complicated UTI with stasis, calculi, pregnancy, neurogenic bladder, and diabetes mellitus
- Laboratory Findings
  - increased WBC, +ve blood culture
  - pyuria and bacteriuria if abscess communicates with collecting system

### What are the radiologic findings associated w/ renal abscess?

- generalized renal enlargement with distortion of the renal contour on affected side
- renal fixation, obliteration of psoas shadow, scoliosis w/ concavity on affected side (spasm)
- nephrogram is delayed or even absent if involvement is diffuse
  - if more localized, the findings may be similar to those of acute focal bacterial nephritis
- renal mass lesion if chronic
  - calyceal system may be poorly defined or show distortion or even amputation
  - relative radiolucency in the involved area on tomograms
- IVP may be normal if abscess involves ant/post kidney w/o impinging parenchyma or collecting system
- U/S: quickest and least expensive → see echo-free or low-echo-density SOL w/ increased transmission
  - surrounding renal parenchyma is edematous
  - # of echoes depends on the amount of cellular debris within the abscess
  - hard to distinguish from tumour
- Arteriography: used infrequently
  - center of mass hypervascular or avascular, with increased vascularity at the cortical margins
- CT = best test
  - well defined both before and after contrast agent enhancement
  - initially: renal enlargement and focal, rounded areas of decreased attenuation



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- a thick fibrotic wall begins to form around the abscess few days later
- echo-free or slightly echogenic mass due to the presence of necrotic debris is seen
- chronic: obliteration of adjacent tissue planes, thickening of Gerota's, round/oval parenchymal mass of low attenuation, surrounding inflammatory wall of higher attenuation (forms a ring with contrast)
  - **ring sign** caused by the increased vascularity of the abscess wall

### What is the treatment for a renal abscess?

- classic treatment = percutaneous or open incision and drainage
- CT/US guided needle aspiration for diagnosis/culture
- if hematogenous dissemination suspected, organism is penicillin-resistant *Staphylococcus*
  - start penicillinase-resistant penicillin
- if abnormal GU tract, usually G-ve
  - start IV third-generation cephalosporins, antipseudomonal penicillins, or AG
- IV antibiotics and careful observation if < 3cm
- 3-5cm (or smaller abscesses in immunocompromised hosts) or those that do not respond to antimicrobial therapy should be drained percutaneously
- **open drainage if > 5cm**

### What is the difference b/w infected hydronephrosis and pyonephrosis?

- *infected hydronephrosis* = bacterial infection in a hydronephrotic kidney
- *pyonephrosis* = infected hydronephrosis with suppurative destruction of the parenchyma of the kidney, in which there is total or nearly total loss of renal function
  - hard to determine where infected hydronephrosis ends and pyonephrosis begins

### What is the clinical presentation for infected hydronephrosis?

- patient is usually very ill, with F/C, flank pain, and tenderness
- previous history of urinary tract calculi, infection, or surgery
- no bacteriuria if ureter completely obstructed

### What are the radiologic findings in infected hydronephrosis?

- urographic findings are those of urinary tract obstruction
- IVP: poorly functioning or non-functioning hydronephrotic kidney in 50%
- U/S best test to dx pyonephrosis – shows 1 of 4 patterns:
  - persistent echoes from the inferior portion of the collecting system
  - fluid-debris level with dependent echoes that shift when the patient changes position
  - strong echoes with acoustic shadowing from air in the collecting system
  - weak echoes throughout a dilated collecting system
- renal pelvis always shows good ultrasonic transmission in infected hydronephrosis
- if U/S not dx, do retrograde: ureteral obstr w/ irregular filling defect in renal pelvis = purulent sediment

### What is the treatment for infected hydronephrosis?

- antibiotics and drainage (stent or NT)

### What is the mortality rate for a perinephric abscess?

- 56% d/t long delay in making diagnosis
  - dx difficult as hx/px non-specific

### What is the cause of perinephric abscess?

- thought to arise from hematogenous seeding from sites of infection, renal extension of ascending UTI
  - located within Gerota's fascia
- if ruptures through Gerota's fascia into the pararenal space, becomes *paranephric abscess*
  - may also result from infectious disorders of the bowel, pancreas, or pleural cavity
- more commonly due to *E. Coli* and *Proteus*, less to *Staph* than in past

### What are the findings in perinephric abscess?

- Clinical
  - classic: cutaneous infection/UTI followed in 1-2 wks by F/C and unilateral flank pain → uncommon
  - most common complaints were F/C, flank or abdominal pain, and dysuria → 1/3 afebrile
  - flank mass in 47%
  - may have DM or stones

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- Bacteriology and Laboratory Findings
  - urine cultures +ve only 1/3 of cases, blood cultures +ve only 1/2 of time
  - WBC increased, N urinalysis

### What are the radiologic findings in perinephric abscess?

- KUB: renal mass, no psoas shadow, no renal outlines, calculi, and retroperitoneal gas → N in 40%
- IVP
  - little or no function: 64%
  - caliectasis or calyceal stretching: 39%
  - calculi: 14%
  - renal displacement: 4%
  - normal: 20%
  - may show a displaced renal fascia
- renal arteriography: may show displacement of renal capsular artery away from the kidney
- **fluoroscopy: N/unoperated kidney should move 2-6cm w/ respirx, but is fixed to surrounding tissues if abscess**
- U/S: diverse appearance → anechoic mass displacing kidney to echogenic collection that blends w/ N echogenic fat w/i Gerota's
- CT: renal distortion and perirenal fluid or gas associated w/ perinephric abscesses → more sensitive than US

### What is the management of a perinephric abscess?

- drainage: primary treatment → medical tx alone doesn't work
  - CT or U/S guided percutaneous aspiration and drainage if small
  - surgical drainage or nephrectomy if the kidney is nonfunctioning or severely infected
  - percutaneous drainage contraindicated in large abscess cavities filled with thick, purulent fluid
- renal cortical abscess or enteric communication require prompt attention

### How does one differentiate b/w perinephric abscess and acute pyelonephritis?

- most patients with pyelo symptomatic for < 5 days, abscess for > 5 days before hospitalization
- acute pyelo pts remain febrile < 4 days once abx started, while all pts w/ perinephric abscess have fever > 5 days (median 7d)
- Note: APCKD patients on HD susceptible to progression from UTI to perinephric abscess

### What is xanthogranulomatous pyelonephritis (XGP)?

- rare, severe, chronic renal infection resulting in diffuse renal destruction → usually unilateral
  - get nonfunctioning, enlarged kidney with obstructive uropathy 2° to nephrolithiasis
  - requires obstruction, UTI, and nephrolithiasis (50% are staghorn)
  - 1° obstruction followed by infx w/ *E. coli*, leading to tissue destruction + collection of lipids by histocytes

### What is the incidence of XGP?

- uncommon: 0.6%-1.4% of patients with renal inflammation who are evaluated pathologically
- is "a great imitator" → misdiagnosed as renal tumour
- peak incidence : 5<sup>th</sup> to 7<sup>th</sup> decade
- women affected 3X as often as men
- 15% diabetic

### What are the pathologic findings in XGP?

- usually unilateral
- divided into three extents of retroperitoneal involvement
  - kidney alone
  - kidney and perinephric fat
  - kidney, perinephric fat, and extensive retroperitoneum
- Gross: yellow-white nodules, pyonephrosis, and hemorrhage
- Micro: xanthoma cells, necrosis and inflammation, and hemosiderin is commonly in the histiocytes
  - lipid-laden macrophages (*xanthoma cells*) distributed in sheets around parenchymal abscesses and calyces and are intermixed with lymphocytes, giant cells, and plasma cells
  - granulomatous process in renal pelvis/calyces that infiltrates, destroys, and replaces renal parenchyma
  - xanthomas cells also in obstructive pneumonia, w/ inflammation and obstruction
  - TCC of renal pelvis also seen
- Cytology: renal xanthoma cells have been seen in 80%

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### What are the findings seen in XGP?

- Clinical
  - flank pain (69%), F/C (69%), and persistent bacteriuria (46%)
  - flank mass (62%), previous calculi (35%)
- Bacteriology and Laboratory Findings
  - *Proteus* #1 (associated w/ stones), *E. Coli* also common
  - 1/3 have –ve urine C&S, 10% have mixed growth
  - infecting organism may be only in tissue culture taken from OR
  - urinalysis: pus and protein
  - anemia, hepatic dysfunction in 50%
  - renal failure: rare, due to unilaterality

### What are the radiologic findings seen in XGP?

- IVP:
  - calculus: 38-70%
  - lack of excretion: 27-80%
  - renal mass: 62%
  - calyceal deformity: 46%
- U/S: enlarged kidney, central echogenic area, increased parenchymal anechoic pattern
- CT is most useful
  - large, reniform mass w/ pelvis surrounding central calcification but w/o pelvic dilatation
  - parenchyma replaced by multiple water-density masses (dilated calyces/abscess cavities filled w/ pus and debris)
  - walls of these cavities enhance w/ contrast: abundant vascularity w/i granulation tissue
    - cavities themselves do not enhance
  - indicate whether adjacent organs or the abdominal wall are involved
- Radionuclide renal scanning w/ <sup>99m</sup>Tc-dimercaptosuccinic acid (<sup>99m</sup>Tc-DMSA)
  - confirm and quantify the differential lack of function
- MR
  - advantages in delineating extrarenal extension of inflammation
  - cystic foci of intermediate intensity signal on T1-images and hyperintensity on T2-weighted images
- arteriography: hyper- and hypo-vascular areas
- often hard to distinguish XGP from RCC

### What is the management of XGP?

- primary obstacle to treatment of XGP is incorrect diagnosis
  - **XGP + hydronephrosis looks just like pyonephrosis**
- usually post-operative diagnosis
- RCC is usual diagnosis, so nephrectomy performed
  - if localized, may be amenable to partial nephrectomy.
- xanthoma cells resemble clear cell adenocarcinoma → difficult to distinguish on frozen section
  - do nephrectomy if can't exclude malignancy
- if diffuse and extensive disease goes to retroperitoneum, must remove of the kidney and perinephric fat
  - dissection of granulomatous tissue from the diaphragm, great vessels, and bowel
  - remove entire mass, as tissue infected in ¾ of pts
- if I&D alone, illness may persist, or develop reno-cutaneous fistula

### What is malacoplakia?

- Greek for “soft plaque”
- unusual inflammatory disease affecting GU/GI tracts, skin, lungs, bones, and mesenteric lymph nodes
  - pts w/ GU malacoplakia have chronic coliform bacteriuria

### What is the cause of malakoplakia?

- unknown
  - coliform infections and compromised health status
  - bacteria (or fragments) form nidus for the CaPO<sub>4</sub> crystals that laminate the *Michaelis-Gutmann* bodies
    - defect in intraphagosomal bacterial digestion accounts for unusual immunologic response

### What are the pathologic findings seen in malakoplakia?

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- large histiocytes, known as *von Hansemann cells* (activated macrophages, lots of pink cytoplasm), and small basophilic, extra- or intra-cytoplasmic calculospherules called *Michaelis-Gutmann bodies* → pathognomonic (although not necessary for the diagnosis)
- EM: intact coliforms (or fragments) w/i phagolysosomes of foamy-appearing malacoplakic histiocytes
- macrophages contain large amounts of immunoreactive  $\alpha_1$ -antitrypsin (AAT)
  - staining for  $\alpha_1$ -antitrypsin important

### What is the clinical presentation of malakoplakia?

- usually > 50 years, F:M 4:1 for malakoplakia w/i GU tract, not w/i other tissues
- patients often are debilitated, are immunosuppressed, and have other chronic diseases
- symptoms of bladder malacoplakia are bladder irritability and hematuria
  - cysto: mucosal plaques or nodules
    - can become fungating, firm, sessile masses that cause filling defects on imaging
- distal ureter may become strictured or stenotic and cause obstruction/nonfunction
- extension into the perirenal space is uncommon
- may get renal vein thrombosis and IVC thrombosis
- testes: epididymo-orchitis
- prostate: rare, but, when it occurs, it may be confused with carcinoma
- mortality > 50%

### What radiologic findings are seen in malakoplakia?

- multifocal
  - IVP: presents as enlarged kidneys with multiple filling defects
    - no renal stones, hydro, or calcification (but, "distal ureter may become strictured or stenotic and cause obstruction"???)
  - U/S: renal enlargement and distortion of the central echo complex
  - CT: foci of malacoplakia are less dense than the surrounding enhanced parenchyma
  - angio: hypovascular mass without peripheral neovascularity
- unifocal
  - IVP: noncalcified mass indistinguishable from other inflammatory or neoplastic lesions
  - CT or U/S: solid or cystic structure → CT best to diagnose extension beyond kidney
  - angio: neovascularity

### What is the management of malakoplakia?

- control of UTI: stabilizes disease
- antibiotics: sulfonamides, rifampin, doxycycline, and TMP because of intracellular bactericidal activity
  - ascorbic acid and cholinergic agents (bethanechol) in conjunction w/ antibiotics
  - **thought to increase intracellular cGMP levels → ?biologic defect causing macrophage dysfunction → EXAM**
- treatment of symptomatic unilateral renal lesions = nephrectomy
- long-term prognosis appears to be related to the extent of the disease
  - if bilateral or occurs in the transplanted kidney, death usually occurs within 6 months
  - if unilateral: long-term survival after nephrectomy

### What is renal echinococcosis?

- parasitic infection caused by the larval stage of the tapeworm *Echinococcus granulosus*
  - in dogs, sheep, cattle, humans in S. Africa, Australia, New Zealand, Mediterranean (Greece), Russia
  - rare in US: seen in **Eastern Europe immigrants** / endemic areas or infection in **SW Indians / Eskimo**

### Describe the life cycle of the *Echinococcus*.

- produced by the larval form of the tapeworm
  - in its adult form resides in the intestine of the **dog, the definitive host**
- ova in dog feces contaminates grass/farmlands, eaten by sheep/pigs/humans (intermediate hosts)
- larvae hatch, penetrate venules in the wall of the duodenum, and are carried to liver
  - if escape liver are carried to lungs
  - 3% of organisms escape and infect the kidneys
- larvae undergo vesiculation, and the resultant hydatid cyst gradually develops at a rate of about 1 cm/yr
  - cyst may take 5 to 10 years to reach pathologic size
- cysts usually single and located in the cortex
- wall of the hydatid cyst has three zones

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- peripheral zone of fibroblasts from tissues of the host becomes the adventitia and may calcify
- intermediate laminated layer becomes hyalinized
- single inner layer of nucleated epithelium: called the *germinal layer*
  - gives rise to brood capsules that increase in number, become vacuolated, and remain attached to the germinal membrane by a pedicle
  - new larvae (scolecex) develop in large numbers from here
  - when brood capsules detach, enlarge + move freely in the fluid and are then called *daughter cysts*

### What are the findings seen in echinococcosis?

- Clinical
  - symptoms those of a slowly growing tumour
  - usually asymptomatic or have a flank mass, dull pain, or hematuria
  - rarely affects renal function
  - can rupture into collecting sys → colic, passage of debris resembling grape skins in urine (hydatiduria)
- Laboratory
  - w/ cyst rupture, daughter cysts in the urine or by identifying the laminated wall of the cyst
  - eosinophilia in < 50%
  - partially purified hydatid arc 5 antigens in a double-diffusion test: most reliable diagnostic test
  - complement fixation, HA, and the Casoni intradermal skin tests less reliable → +ve in 90%

### What radiologic findings are seen in echinococcosis?

- IVP: thick-walled cystic mass, occasionally calcified
  - if ruptures into collecting system, daughter cysts may be outlined in pelvis as irregular mass
- U/S: multicystic or multiloculated mass, bright falling echoes from hydatid sand
- CT: several patterns
  - most specific: cystic mass w/ discrete, round daughter cysts + well-defined enhancing mmb
  - less specific pattern: thick-walled multiloculated cystic mass
  - presence of daughter cysts within the mother cyst differentiates the lesion
- do not aspirate: danger of rupture, spillage of highly antigenic cyst contents → fatal anaphylaxis

### What is the management of echinococcosis?

- medical – benzimidazole compounds such as mebendazole → significant side effects
- surgery – mainstay of treatment
  - remove without rupture
  - if cyst wall is calcified, larvae are probably dead and risk of seeding is low
  - if cyst ruptures or can't be removed, fill cyst with 30% NaCl, 2% formalin or 1% iodine for 5 minutes to kill epithelium

### What is the definition of sepsis vs. septic shock?

- septic shock = sepsis syndrome + hypotension
  - septic shock is consequence of gram-negative bacterial infection
    - may also be caused by G+ve organisms and fungi and, probably, by viruses
- sepsis = evidence of inadequate organ perfusion, including one or more of the following:
  - hypoxemia, elevated plasma lactate concentration, oliguria
  - clinical evidence of infection, RR>20, HR>90, hyper/hypothermia

### What is the mortality of sepsis or septic shock?

- sepsis ~ 13%, sepsis presenting with shock ~ 28%, shock developing after sepsis ~ 43%

### What is the cause of hypotension and toxicity in septic shock?

- central role of macrophages, endothelium, and cytokines
- Bacterial Cell Wall Components in Septic Shock
  - exotoxins made by some bacteria (ex: exotoxin A made by *P. aeruginosa*) can initiate septic shock
  - bacteria themselves and cell walls also responsible
  - prime initiator of G-ve bacterial septic shock is endotoxin (LPS component of bacterial outer mmb)
  - outermost part of endotoxin molecule are oligosaccharides responsible for O serotype of G-ve bact
    - inside of these are core oligosaccharides
  - Lipid A bound to the core oligosaccharide → responsible for most of the toxicity
- Antibodies to Endotoxin
  - antibodies to O side chains inhibit the effects of endotoxin

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- Cytokine Network
  - monocytes remove and detoxify LPS
  - also make TNF, IL-1 → overproduction causing syndrome
- TNF — central mediator of pathophysiological changes associated with release of LPS
- IL-8 and IL-10 are being evaluated as possible important mediators in shock

### What is the clinical presentation of pts w/ sepsis?

- classic: F/C followed by hypotension → in about 30% patients with G-ve bacteremia
- earliest sign: tachypnea and respiratory alkalosis
- change in mental status (lethargy or obtundation)
- bull's-eye lesion associated with *P. aeruginosa* may be identified

### What is the etiologic agent in sepsis?

- G-ve bacteria → 30-80%
- G+ve bacteria → 5-24%
- *E. Coli* (1/3), *P. aeruginosa*, *Proteus*, *Providencia*, and *Serratia*

### What is the mortality of pts in sepsis?

- mortality: 10-90%
  - 40% of deaths occurred within 24 hours and 60% within 48 hours
- antimicrobial treatment decreases the frequency of shock and improves survival rates

### What factors are associated with a high probability of bacteremia?

- fever, WBC count, Cr level, DM, and low serum albumin
- sepsis and death more prevalent if these are present

### What is the management of pts w/ sepsis?

- blood C&S, culture all sources
- use AG if GU tract most probable source
- if hospital acquired, or if the pt has multiple infections or is immunocompromised or severely ill:
  - AG and anti-*Pseudomonas* pen (carbenicillin, ticarcillin, piperacillin) or 3<sup>rd</sup>-gen cephalosporin used
- continue antibiotic until the patient has been afebrile for 3 to 4 days and clinically stable
- when stable, source of bacteremia must be sought and adequately treated

### What is the incidence of uncomplicated cystitis?

- occurs in pts w/o abnormalities of the GU tract, in the absence of recent GU surgery/instrumentation
  - occasionally occurs in prepubertal girls
  - increases greatly in incidence in late adolescence and during the 2<sup>nd</sup> and 4<sup>th</sup> decades
  - prevalence: 25% to 30% of women between the ages of 20 and 40 have had a UTI

### What are the risk factors for uncomplicated UTI?

- sexual intercourse and use of condoms
- young men: occasional acute cystitis w/o underlying structural or functional abnormalities
  - often assoc with not being circumcised, with sexual activity, or with HIV infection

### What is the etiologic agent in cystitis?

- *E. coli* in 80%, and *S. saprophyticus* in 5% to 15%
- rare: *Klebsiella*, *Proteus*, or enterococci
- men: *E. coli* and other Enterobacteriaceae

### What is the clinical presentation of a UTI?

- dysuria, frequency, urgency, voiding of small urine volumes, and SP/lower abdo pain
- hematuria, foul-smelling urine
- males: urethral discharge and dysuria

### How can one diagnose a lower tract infection?

- based on U/A with bacteriuria, pyuria, and hematuria
- nitrite and leukocyte esterase dipstick tests less sensitive than microscopic examination of urine
- urine culture is definitive test
  - in symptomatic patients,  $> 10^2$  cfu/ml of urine = infection

## Chapter 14 Questions - UTIs.doc

- if hx suggests acute cystitis w/o complicating factors with +ve U/A for WBC, RBC, or bacteria, may treat w/o culture

### What are the indications for pre-treatment urine C&S for cystitis?

- recent antimicrobial therapy or UTI symptoms for greater than 7 days
- age older than 65 years
- diabetes
- pregnancy
- pre-treatment urine C&S in all men
- uncertainty regarding dx

### What is the differential diagnosis of a UTI?

- vaginitis
  - hx: irritative voiding with vaginal irritation
    - subacute in onset
    - vaginal discharge/odor
    - multiple or new sexual partners
    - no freq/urge/dysuria/SP pain
  - px: vaginal d/c w/ inflammatory cells
- urethral infections caused by STD
  - HSV, gonorrhea, *Chlamydia*, trichomoniasis, yeast, and BV
  - urethritis
    - subacute dysuria
    - history of discharge and new or multiple sexual partners
    - less severe freq/urge, no F/C
    - ++ urethral discharge w/ pus cells
- miscellaneous noninflammatory causes of urethral discomfort
  - trauma, chemical irritants, or allergy

### What is the treatment for a UTI?

- Healthy women
  - Ciprofloxacin 500mg PO q12h x 3d
  - Enoxacin 400mg PO q12h x 3d
  - Levofloxacin 500mg PO qd x 3d
  - Lomefloxacin 400mg PO qd x 3d
  - TMP-SMX 160-800mg PO q12h x 3d
  - TMP 100mg PO q12h x 3d
  - Microcrystalline nitrofurantoin 100mg PO QID x 3d
  - Norfloxacin 400mg PO q12h x 3d
- Sx >7 days, recent UTI, >65 yr, DM, diaphragm use
  - TMP-SMX or Fluoroquinolone q12h x 7d
- Pregnancy
  - Amoxicillin 250mg PO q8h x 7d
  - Cephalexin 500mg PO QID x 7d
  - Microcrystalline nitrofurantoin 100mg PO QID x 7d
  - TMP-SMX 160-800mg PO q12h x 7d
- Men, healthy and < 50 years old
  - TMP-SMX or Fluoroquinolone q12h x 7d

### What is the level of resistance to each antibiotic?

- Septra: R of 9-18% → TMP just as good as TMP/SMX, decreased s/e
  - eradicates E. Coli from vagina → nitrofurantoin and  $\beta$ -lactams don't
- 1/3 cystitis bact R to amoxicillin, cephalothin, and sulfonamides, 15%-20% R to nitrofurantoin
- amoxicillin-clavulanate and the cephalosporins → #1 choice in pregnancy
- fluoroquinolones: use where prevalence of R to TMP-SMX or TMP is 20% or greater
  - quinolones should be used primarily for treatment failures (unresolved UTIs)
  - also if allergies to other drugs, recurrent infections, and if known resistance
  - use quinolone if known populx resistance to TMP > 20%

### How long does one treat a UTI?

## Chapter 14 Questions - UTIs.doc

- 3-day = 7-day regimens – fewer s/e and lower cost
- single dose OK, but increased recurrence, decreased cure
  - esp w/ amoxicillin and cephalosporins, as rapid excretion
- young healthy men: 7-day regimen of TMP-SMX, TMP, or a fluoroquinolone
- no F/U visit or culture necessary unless symptoms persist or recur
  - then, do U/A and urine C&, treat for 7 days with a fluoroquinolone
  - need F/U visit and culture in older women, if potential risk factors, and in men
  - evaluation unnecessary in women, usually unnecessary in young men who respond to therapy

### What is the most common source for recurrent UTIs?

- most commonly new infections from bacteria outside the urinary tract (reinfection)
  - persistence is uncommon
    - cure by removing focus of bacteria
  - women w/ reinfx usually have no underlying GU abnormality → need long-term medical management
  - men: uncommon → may be associated with underlying abnormalities (ex: stricture)
    - cysto all men w/ recurrent UTI

### What are the risk factors for recurrent UTI in women?

- first UTI before age 15 years
- maternal history of UTI
- diaphragm-spermicide & tampon use → increases risk of UTI/vaginal colonization with *E. coli*
  - spermicides w/ nonoxynol-9: ?reduction in vaginal lactobacilli
  - stop all spermicides in women w/ recurrent UTI
- postmenopausal
  - etiology: PVR, often w/ bladder/uterine prolapse
    - decreased estrogen changes vaginal microflora → decreased lactobacilli
      - ◆ if replace estrogen, can decrease UTI

### What are the indications for IVP in recurrent UTI?

- unexplained hematuria, obstructive symptoms, neurogenic bladder dysfunction, renal calculi, fistula, analgesic abuse, DM

### What are the indications for cystoscopy in recurrent UTI?

- in men or women w/ frequent reinfections and sx of obstruction, bladder dysfunction, fistula

### How can one treat recurrent UTI?

- Low-Dose Prophylaxis: given to prevent reinfection
  - if kill bacteria in bowel/vag, effective for prophylaxis of UTIs
  - increase in resistant strains w/ even short course antibiotics
- Postintercourse Prophylaxis
  - single dose of nitrofurantoin, cephalexin, or TMP-SMX reduces incidence of reinfection
- Intermittent Self-Start Therapy
  - Self-administered, single-dose therapy: women identify infection from symptoms and treat themselves at the onset
  - Self-diagnosis and self-start therapy
    - patient given dip-slide device for culture if UTI occurs
    - pt starts 3-day course of broad-spec antibiotic (w/o fecal flora effects) immediately after culture
      - ◆ fluoroquinolones are ideal (nitrofurantoin and TMP-SMX are OK, but less effective)
      - ◆ don't give tetracycline, ampicillin, sulfamethoxazole, and cephalexin → develop R
    - culture then brought to office: if no response, repeat culture
    - if –ve culture w/ ++ symptoms, r/o CIS, IC, neurogenic bladder

### What drugs are effective in treatment of recurrent UTI?

- Trimethoprim-Sulfamethoxazole
  - eradicates G-ve's from gut + vaginal fluid
  - gut is a reservoir for organisms that may colonize the periurethral area
  - TMP infuses across noninflamed vag, produces conc above serum levels
- Trimethoprim
  - as effective as TMP-SMX for prophylactic prevention of recurrent UTIs
  - patients treated for long periods w/ TMP developed coliforms resistant to TMP
- Nitrofurantoin



## Chapter 14 Questions - UTIs.doc

- does not alter the gut flora
- brief high concentrations in urine → repeated elimination of bacteria
- minimal fecal resistance (~2%) 2° to complete absorption in GI tract or degradation/inactivation
- colonization of introitus with Enterobacteriaceae continues throughout therapy
- side effects:
  - acute pulmonary reactions (43%)
  - allergic reactions (42%)
  - neuropathy, blood dysurias, liver damage, and chronic pulmonary reactions
  - risk increases with age → most if > 50 years → monitor if long-term therapy
- Cephalexin
  - 125 mg cephalexin/day as effective as 250 mg/day
  - excellent prophylactic agent because fecal resistance does not develop at this low dosage
- Fluoroquinolones
  - eradication of Enterobacteriaceae from the fecal and vaginal flora
  - eradicates periurethral and fecal colonization with aerobic G<sup>-ve</sup> organisms
  - *only if R or pt intolerance to TMP-SMX, TMP, nitrofurantoin, or cephalexin*

### What is the efficacy of prophylaxis for recurrent UTI?

- recurrences decreased by 95% when compared with placebo
- reduction in reinfection rate from 2.0-3.0 per pt-year to 0.1-0.4 per pt-year
- requires only small dose at bedtime x 6-12 months
- if reinfection during therapy, start full dose, then prophylaxis when treated

### What is the management of recurrent UTI due to bacterial persistence?

- represent the only surgically curable cause of recurrent UTI
- require systematic radiologic and endourologic evaluation
  - excretory urography and cystoscopy - initial screening
  - CT and bacterial localization cultures if indicated
    - ex: *Proteus* infections require CT and tomograms
    - if ID upper tract abnormality, may be source of bacterial persistence → ureteral catheterization
    - if chronic bacterial prostatitis suspected, do LUT localization studies
  - if focus of infection cannot be eradicated, long-term antibiotics

### What is the incidence of bacteriuria in women?

- 3%-6% of sexually active women of childbearing age are bacteriuric (ScBU)

### Are adult women with screening bacteriuria at risk of serious renal damage?

- No → 69% have bladder irritative sx w/i 1 year (vs. 18% of non-bacteriuric pts)
  - IVP on bacteriuric pts: 34% abnormal (minor scars, small calculi, hydroureter/nephrosis)
    - none had renal cortical destruction, no evidence of htn, ARF, renal scarring 3-5yrs later

### Do women with screening bacteriuria differ from those with symptomatic bacteriuria?

- Yes → probability of symptomatic infection 7X greater in women with known ScBU than in those without
  - only 1/3 of pts have continuous ScBU

### Is detection of screening bacteriuria in adult women a worthwhile public health effort?

- two requirements for a useful screening procedure
  - detects disease before irreversible damage has occurred
  - disease detected may be effectively treated
- disease under study should be serious enough that detection worthwhile
- **screening for bacteriuria in 1<sup>st</sup> trimester of pregnancy only time that screening is worthwhile**

### What is the urethral syndrome?

- historical term only → refers to any sx or combo of sx suggestive of UTI in patients considered to be uninfected: see Ch.16
- three subgroups of pts:
  - syndrome with an infectious (microbial) cause, almost always w/ inflammatory response
  - interstitial cystitis, rarely accompanied by inflammatory cells
  - “pure” urethral syndrome (includes pts w/o infx or IC)
- exclude urethral/vaginal infection, then r/o IC

## Chapter 14 Questions - UTIs.doc

- once IC excluded, pt has "pure" urethral syndrome → usu emotional basis for their discomfort
- vaginal inclusion epithelium covering the trigone and urethra is a normal embryologic development → is not "squamous metaplasia", "trigonitis" or "urethrotrigonitis"

### What are the anatomic and physiologic changes to the GU tract during pregnancy?

- pregnant women to be more susceptible to pyelonephritis and may require alteration of therapy
- Increase in Renal Size
  - renal length increases approximately 1 cm → increased renal vascular and interstitial volume
- Smooth Muscle Atony of the Collecting System and Bladder
  - decreased peristalsis during pregnancy
  - most women in 3<sup>rd</sup> trimester show significant ureteral dilatation
    - muscle-relaxing effects of increased progesterone during pregnancy
    - **mechanical obstruction of the ureters by the enlarging uterus**
- Bladder Changes
  - bladder becomes hyperemic
  - estrogen causes bladder hypertrophy & squamous changes of the urethra
- Augmented Renal Function
  - increases in GFR by 30-50% and increased renal plasma flow & protein excretion, decreased Cr and BUN
- Pathogenesis
  - adhesin-based mechanism of pyelonephritis-induced preterm births and low birth weights
  - systemic spread of the Dr adhesin +ve *E. coli* to the placentae and fetuses
  - upregulation of Dr adhesin in kidney, endometrium, and placenta during 3<sup>rd</sup> trimester

### Why does one screen for bacteriuria during pregnancy?

- prevalence of bacteriuria in screening pregnant females (ScBUP) same as in nonpregnant females (4-6%)
- 1-2% develop bacteriuria during pregnancy
- increased rates w/ duration of pregnancy, lower socioeconomic class, multiparity, and sickle-cell traits
- site of bacteriuria
  - site of infection unrelated to likelihood that pyelonephritis will develop during pregnancy
  - localization to upper tracts may ID women who are likely to have persistent postpartum bacteriuria

### What is the natural history of bacteriuria during pregnancy?

- pregnant females w/ bacteriuria at **high risk of suffering recurrent bacteriuria** w/ or w/o treatment
  - of pregnant women w/ bacteriuria
    - 18%: develop acute pyelonephritis
    - 13.5%: spontaneously cleared their infection
    - 66%: remained bacteriuric
- risk of recurrent infection in pregnant women independent of duration of antimicrobial therapy and infx site
- **incidence of acute pyelo in pregnant women w/ bacteriuria significantly increased over nonpregnant women**
  - occurs in 1% to 4% of all pregnant women
  - **13.5% to 65% of women with ScBUP developed acute pyelonephritis during pregnancy**
- if develop pyelo, 60-75% develop in 3<sup>rd</sup> trimester → hydronephrosis/stasis in GU tract most pronounced
  - 10% to 20% of women who get pyelo in pregnancy get it again
  - 1/3 of pregnant women w/ pyelo have past hx of pyelo
  - tx of ScBUP decreases pyelo during pregnancy from 13.5%-65% to 0%-5.3%
- women w/ persistent bacteriuria may have increased incidence of impaired CrCl and urinary concentrating ability, and an increased incidence of radiographic changes suggestive of chronic pyelo
  - F/U IVP in pregnant women w/ bacteriuria: 8%-33% incidence of changes compatible w/ chronic pyelo
- 10% of pregnant women have radiologic evidence of pyelo on IVP
  - highest in women w/ infections localized to upper tracts
- uncomplicated bacteriuria in pregnant women doesn't produce changes in kidney appearance or function different from those found in nonpregnant bacteriuric women

### What complications are associated with bacteriuria during pregnancy?

- Prematurity and Perinatal Mortality
  - not known if pyelonephritis/ScBU during pregnancy increases prematurity and perinatal mortality
  - if antepartum renal infections treated, whether symptomatic or not, did not affect pregnancy outcome
  - only placental growth retardation increased in frequency in pregnant women with pyuria and bacteriuria
- Maternal Anemia

## Chapter 14 Questions - UTIs.doc

- untreated bacteriuria increases the likelihood of developing anemia during pregnancy
  - pregnant patients requiring > 3 treatments for bacteriuria have lower Hgb levels
  - 14.6% of bacteriuric women vs. 10% anemic at the first prenatal visit
  - 3<sup>rd</sup> trimester: 25% vs. 16.8%

### How does one manage bacteriuria during pregnancy?

- Diagnosis of Bacteriuria
  - risk of bacteriuria increases with the duration of pregnancy
  - if initial is –ve, can repeat at 16wks if hx UTI/VUR
  - don't catheterize pregnant women to get urine
- Treatment of UTI during Pregnancy
  - 3-day course, w/ reculture at 1-2 days
  - severe pyelonephritis requiring hospitalization - IV until afebrile, then PO for 14d total
  - pregnant women w/ pyelo → must admit for IV antibiotics
    - most respond w/i 24h w/ IV amp/AG
    - if don't respond, r/o obstruction/abscess
    - must monitor for pyelo later in pregnancy
- Pregnancy in Women with Renal Insufficiency
  - need Cr and CrCl prior to pregnancy
  - mild renal disease: OK
  - severe renal disease: complicated in all cases
    - increased prematurity, C-section, htn, worsening proteinuria / renal insufficiency during pregnancy

### What antibiotics are safe or unsafe during pregnancy?

- unsafe
  - tetracyclines: acute maternal liver decompensation and fetal malformations
    - hypoplasia and staining of the child's deciduous teeth
  - erythromycin: cholestatic jaundice in pregnant females
  - chloramphenicol: "gray baby syndrome" → CVS collapse and high neonatal mortality
  - fluoroquinolones: potential adverse effects on cartilage formation
  - sulfa: neonatal hyperbilirubinemia and kernicterus
    - safe in 1<sup>st</sup> 2 trimesters → fetus in utero handles unconjugated bilirubin through placenta
- safe
  - Ampicillin 500 mg qid
  - Amoxicillin 250 mg tid
  - Penicillin V 500 mg qid
  - Cephalexin 500 mg qid
  - Cefaclor 500 mg qid
  - Nitrofurantoin 100 mg qid
    - can cause hemolytic anemia in pts and fetuses with a G6PD deficiency
    - contraindicated at term: hemolytic anemia in neonates w/ immature enzyme system

### Why are the elderly at increased susceptibility to UTI?

- changes of aging
  - decline in cell-mediated immunity
  - altered bladder defenses owing to obstructive uropathy
  - neurogenic dysfunction
  - increased receptivity of uroepithelial cells
  - increased risk of contamination 2<sup>o</sup> to fecal/urinary incontinence, urethral instrumentation/catheterization
  - decrease in prostatic/vaginal antibacterial factors 2<sup>o</sup> to changes in pH and levels of zinc and hormones
- acquired abnormalities of GU tract
- increased exposure to environmental / therapeutic risk factors

### What is the prevalence of UTI in the elderly?

- prevalence of UTIs in elderly is much higher than in younger people
- 20% of women and 10% of men older than 65 years have bacteriuria
- ratio progressively decreases to 2:1 F:M
- asymptomatic bacteriuria among elderly women 17-55% - increases w/ age and concurrent disease

### What is the clinical presentation of UTI in the elderly?

## Chapter 14 Questions - UTIs.doc

- most elderly have no urinary tract symptoms → high index suspicion if RF present
- lethargy, confusion, anorexia, and incontinence
- pyuria not good predictor of bacteriuria in this pplx  
→ absence of pyuria is good predictor of the absence of bacteriuria
- $10^3$  or more bacteria / mL good predictor for significance
- evaluation: Cr, IVP, U/S, UDS, and/or cystoscopy

### What is the etiologic agent for UTIs in the elderly?

- *E. coli* causes only 75% of these infections
- *Proteus*, *Klebsiella*, *Enterobacter*, *Serratia*, *Pseudomonas* species and enterococci also
- G+ve more common in elderly men than women
- due to increased institutionalisation, hospitalization, catheterization, and antimicrobial use

### What is the significance of a UTI in the elderly?

- UTI w/ underlying structural GU abnormalities or systemic conditions (ex: DM)  
→ can lead to renal failure
- significance of asymptomatic bacteriuria (not from urea-splitting bacteria) is controversial
- bacteriuria in the absence of obstruction rarely, if ever, progresses to renal failure
- bacteriuria also associated w/ increased mortality  
→ either direct effect on mortality of the bacteriuria itself or from underlying disease that increase both bacteriuria and mortality  
→ treatment will reduce mortality only if bacteriuria is the direct cause

### How does one manage UTIs in the elderly?

- elderly more susceptible to toxic and adverse effects of antibiotics  
→ metabolism and excretion of antimicrobial agents may be impaired
- symptomatic UTIs should be treated

### What are the indications for treatment of asymptomatic bacteriuria?

- none: ? tx of urease splitting organism  
→ elderly, *nonhospitalized* women: short course eliminates bacteriuria for 6 months in 2/3 pts  
→ *institutionalized* elderly women: no difference – don't treat if no obstruction

### What is the prevalence of UTIs in pts w/ SCI?

- most common urologic complications of spinal cord injury (SCI)  
→ 33% of SCI patients have bacteriuria at any time, eventually all will become bacteriuric
- most common cause of fever in the SCI patient

### Why do pts w/ SCI get UTIs?

- overdistention of the bladder
- elevated intravesical pressure
- increased risk of urinary obstruction
- VUR
- impaired voiding
- instrumentation
- increased incidence of stones
- decreased fluid intake
- poor hygiene
- perineal colonization
- decubiti and other evidence of local tissue trauma
- reduced host defense associated with chronic illness

### What is the clinical presentation of a UTI in a pt w/ SCI?

- majority asymptomatic
- usually no frequency, urgency, or dysuria since loss of sensation
- flank, back, or abdominal discomfort, leakage b/w catheterizations, increased spasticity, malaise, lethargy, and/or cloudy, malodorous urine
- UTI is most common cause of fever in SCI pts

### What are the laboratory findings in pts w/ SCI and UTI?

## Chapter 14 Questions - UTIs.doc

- U/A: bacteriuria and pyuria
  - pyuria doesn't = infection → may occur from irritative effects of catheter
- urine C&S
  - most pts w/ catheter & low-level bacteriuria increase to  $> 10^5$  cfu/ml quickly
  - if on CIC,  $10^2$  cfu/ml significant
  - if catheter-free,  $10^4$  cfu/ml was considered significant
- Etiology:
  - *E. coli* (20%)
  - *Enterococci*, *Proteus*, and *Pseudomonas* are more common
  - also see *Klebsiella*, *Serratia*, *Staphylococcus*, and *Candida*
  - short term cath: usually 1 organism
  - long-term: polymicrobial
  - 2 most persistent species: *E. coli* and *Providencia stuartii*

### How does one manage a UTI in the pt w/ SCI?

- urine C&S before starting treatment from ++ resistance
  - quinolone if afebrile
  - $\beta$ -Lactams, TMP-SMX, and nitrofurantoin not recommended since ++ R
- change catheter
- if F/C, admit for IV pen/AG
  - 4-5d if mild, 10-14d if very sick
- if no improvement in 24-48h, reculture
  - imaging studies to r/o stones, obstruction, abcess
- post-treatment cultures not usually helpful → only if urea-splitting organism present
- if recurrent, need imaging and UDS, w/ review of bladder management
  - discuss catheter drainage, CIC techniques and frequency, voiding schedule
  - may be associated w/ high voiding pressures
    - intervention to decrease pressures may decrease incidence of UTI
- cath for  $> 10y$ : increased risk of carcinoma of the bladder
  - etiology: chronic infection and inflammation, ?nitrosamines produced in infected urine

### What is Fournier's gangrene?

- necrotizing fasciitis occurring about the male genitalia
- abrupt onset of a rapidly fulminating genital gangrene of idiopathic origin
- infection most commonly arises from the skin, urethra, or rectal regions
  - association w/ urethral obstruction from strictures and extravasation and instrumentation

### What are the RF for Fournier's?

- diabetes mellitus
- local trauma
- paraphimosis
- periurethral extravasation or urine
- perirectal or perianal infections
- surgery such as circumcision or herniorrhaphy

### What is the presentation of the pt w/ Fournier's?

- Clinical
  - history of recent perineal trauma, instrumentation, urethral stricture from STD, urethral cutaneous fistula
  - pain, rectal bleeding, history of anal fissures suggest a rectal source
  - commonly starts as cellulitis adjacent to the portal of entry
  - swollen, erythematous, and tender
  - pain, fever, systemic toxicity
  - swelling and crepitus of scrotum → gangrene
  - if obese diabetic + abdo wall involvement = ++ rapid spread
  - dysuria, urethral discharge, and obstructed voiding
  - G+ve sepsis: change in LOC, tachypnea, tachycardia,  $T > 101^\circ\text{F}$  or  $< 96^\circ\text{F}$
- Laboratory Studies
  - anemia: decreased functioning RBC mass from thrombosis and sepsis
  - increased Cr, hyponatremia, and hypocalcemia
    - hypocalcemia from bacterial lipases: destroy TriG and release FFA that chelate  $\text{Ca}^{2+}$

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### What other diagnostic studies are helpful in the pt w/ Fournier's?

- AXR: air in abdo wall
- scrotal U/S
- ulcer biopsy: superficially intact epidermis, dermal necrosis, vascular thrombosis  
→ PMN invasion w/ subcutaneous tissue necrosis

### How does one manage the pt w/ Fournier's?

- marked systemic toxicity out of proportion to the local finding
- IV hydration, antibiotics (amp/ceftriaxone), debridement
- extensive excision to normal tissue, leave wound open
- 2<sup>nd</sup> OR 24-48h later
- no orchiectomy, as testes have good blood supply from gonadal arteries
- SP tube if urethral involvement
- colostomy if rectal/sigmoid involvement
- hyperbaric O<sub>2</sub> may help

### What is the prognosis for the pt w/ Fournier's?

- mortality ~20%, ranges from 7-75%  
→ increased mortality if: DM, alcoholics, colorectal sources (atypical presentation, greater delay in dx, widespread extension)

### What is a periurethral abscess?

- life-threatening infection of the male urethra and periurethral tissues
- small and localized by Buck's initially
- when Buck's penetrated, ++ necrosis of the subcutaneous tissue and fascia  
→ fasciitis spreads as far as the buttocks posteriorly and the clavicle superiorly

### What is the cause of periurethral abscess?

- 2<sup>o</sup> to gonorrhea, urethral stricture disease, urethral catheterization or instrumentation
- source if infection is urine
- G<sup>-ve</sup> rods, enterococci, and anaerobes are most frequent – often multiple organisms or anaerobes

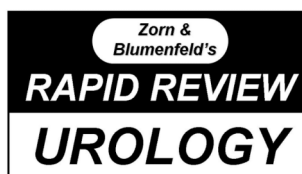
### What is the clinical presentation of pts w/ periurethral abscess?

- scrotal swelling (94%)
- fever (70%)
- acute urinary retention (19%)
- spontaneously drained abscess (11%)
- dysuria or urethral discharge (5% to 8%)
- usually 3/52 b/w symptom onset and presentation
- U/A: pyuria and bacteriuria

### What is the management of the periurethral abscess?

- immediate suprapubic urinary drainage and wide débridement
- antibiotics: AG and cephalosporin
- perineal urethrostomy or chronic SP diversion occasionally has been helpful to prevent recurrence
- bx to r/o malignancy





## **Chapter 15**

### **• Prostatitis and Related Conditions •**

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#### **What is the most common urologic diagnosis in men < 50 yrs?**

- prostatitis → 8% of GU office visits
  - 3<sup>rd</sup> most common GU dx in men > 50 years (after BPH and prostate cancer)
  - 5% of men 20-50 yrs have hx of prostatitis

#### **What is the incidence of prostatitis?**

- Ureplik Study: 35% of men had ≥ 1 sx of prostatitis over past year
- Lennox and Addington County study: 9.7% of all men have pain/discomfort in perineum or w/ ejaculation or both
- Olmsted County study: prostatitis affects men of all ages
  - compared with men aged 66 years and older, the odds of a prostatitis diagnosis:
    - 1.6 X greater if 18 to 35
    - 2.6 X greater if 36 to 50
    - 2.1 X greater if 51 to 65
  - age-specific prevalence of prostatitis highest if 20-49yrs or > 70yrs
  - accumulative probability of getting prostatitis (acute or chronic) by 85yrs = 26%

#### **What is the definition of prostatitis?**

- increased number of inflammatory cells w/i prostatic parenchyma
  - prostatic inflammation may (or may not) be noted in patients with a diagnosis of prostatitis

#### **What are the pathologic findings seen in pts w/ prostatitis?**

- lymphocytic infiltrate in stroma adjacent to prostatic acini – most common pattern
  - ranges from scattered lymphocytes to dense lymphoid nodules
    - lymphocytes + scattered plasma cells w/i fibromuscular stroma w/o relx to ducts/acini
    - inflammatory cells restricted to glandular epithelium and lumen: found in prostatitis / BPH
- prostatic calculi can increase prostatic inflammation
  - obstructing central prostate ducts → preventing drainage, providing a nidus for infection
- granulomatous prostatitis: non-specific/variable histologic pattern
  - heavy lobular, mixed, inflammatory infiltrates w/ ++ histiocytes, lymphocytes, and plasma cells
  - may have small discrete granulomas

#### **What are the various proposed etiologies of prostatitis?**

- Microbiologic
  - Gram -ve bacteria
    - *Enterobacteriaceae*: most common cause of bacterial prostatitis → originate in GI flora
      - ◆ *Escherichia coli*: 65% to 80% of infections
    - *Pseudomonas*, *Serratia*, *Klebsiella*, *Enterobacter* in 10%-15%
    - virulence factors play a role: P-pili, type 1 pili, biofilm formation
  - Gram +ve bacteria
    - Enterococci in 5-10% of documented prostate infections
    - *S. saprophyticus*, hemolytic strep, *S. aureus*, and other coagulase-negative staph implicated
      - ◆ coagulase-negative *Staph* in EPS and transperineal prostate bx tissue of men with CP
  - Anaerobic Bacteria: role of anaerobic bacteria is unknown
    - *Corynebacterium*: could be missed by routine culturing of EPS
    - *Chlamydia*: controversial
      - ◆ 1/3 men w/ CP have Ab to *C. trachomatis* compared with 3% controls
      - ◆ many studies not able to culture or detect Chlamydia in CP pts
    - *Ureaplasma urealyticum*: often seen in urethras of men w/ and w/o non-specific urethritis



## Chapter 15 Questions - Prostatitis.doc

- other microorganisms: *Candida* and other mycotic infections (aspergillosis and coccidioidomycosis) implicated
  - ◆ viruses: no evidence
  - ◆ *Trichomonas* also seen
- Nonculturable Microorganisms
- Altered Prostatic Host Defense
  - pts may have RF that allow bacterial colonization or infection of the prostate (see below)
  - secretory dysfunction of prostate may adversely affect normal antibacterial nature of prostatic secretions
    - decreased fructose, citric acid, acid phosphatase, Zn, Mg, Ca, prostatic antibacterial factor
    - increased pH, inflammatory proteins ceruloplasmin and complement C3
- Dysfunctional Voiding
  - high-pressure dysfunctional flow patterns implicated in causing prostatitis **via intraprostatic ductal reflux**
- Intraprostatic Ductal Reflux
  - reflux of urine +/- bacteria into prostatic ducts → most important mechanism in chronic prostatic inflammation
  - peripheral zone more susceptible than other zones
  - bacteria that reflux into prostate may live in protected aggregates in prostatic calculi
- Immunologic Alterations
  - acute bacterial prostatitis: serum/prostatic fluid Ag-specific Ig detected immediately after infx onset
    - decline to normal levels over 6-12 months w/ successful antibiotics
    - PSA increases during acute infection, decrease over 6 weeks
  - chronic prostatitis: no serum Ig elevation, prostatic fluid IgA and IgG levels are both increased
    - IgG normalizes after several months, but IgA (esp. SIgA) elevated for almost 2 years
  - may be 2° to immunologically mediated inflammation from unknown Ag or autoimmune process
    - IgA, IgM, fibrinogen, complement C3 in prostatic biopsies in CP
- Chemically Induced Inflammation
  - urine and metabolites (ex: urate) present in prostatic secretion of patients with CP
  - ? chemically induced inflammation 2° to noxious substances in urine refluxing into prostatic duct
- Neural Dysregulation
  - acquired abnormalities in CNS: insufficient conscious control of pelvic floor muscles
- Pelvic Floor Musculature Abnormalities
  - source of pain at pelvic musculature attachment at sacrum, coccyx, ischial tuberosity, pubic rami, and endopelvic fascia
    - hyperirritable spot or myofascial trigger point that is painful on compression
- Interstitial Cystitis-like Cause
  - pain and voiding symptoms of interstitial cystitis and CP overlap
  - men with CP have cystoscopic + UDS findings similar to patients with IC
- Psychological Cause
  - important role in the development or exacerbation → ? view as a psychosomatic disorder
  - depression and psychological disturbances are common among CP patients
- Interrelated, Pluricausal, Multifactorial Etiology
  - initiating stimulus starts cascade: infection → reflux of toxic/immunogenic urine substance → perineal or pelvic “trauma”
  - local response: inflammation or neurogenic injury
  - final outcome: clinical manifestation of chronic perineal or pelvic pain

### How do virulence factors play significant role in pathogenesis of prostatitis?

- bacterial P-fimbria: bind to urothelial receptors, facilitates ascent into the GU tract
- type 1 fimbria (*mannose-sensitive fimbriae*) – present in prostatitis
  - phase variation of type 1 pili may occur in the setting of prostatitis
- bacteria reside deep in prostate ducts
  - tend to form aggregates (or *biofilms*) → allows bacteria to persist in prostate even w/ antibiotics

### What risk factors allow bacterial colonization / infection of the prostate?

- intraprostatic ductal reflux
- phimosis
- specific blood groups
- unprotected penetrative anal / rectal intercourse
- UTI
- acute epididymitis
- indwelling urethral catheters and condom catheter drainage
- transurethral surgery, especially in men who have untreated, infected urine

## Chapter 15 Questions - Prostatitis.doc

### What are the potential causes for formation of myofascial trigger points in the pelvis?

- mechanical abnormalities in the hip and lower extremities
- chronic holding patterns such as those that occur during toilet training
- sexual abuse
- repetitive minor trauma and constipation
- sports that create chronic pelvic stimulation
- trauma or unusual sexual activity
- recurrent infections
- surgery

### How can one classify prostatitis?

- Meares-Stamey four-glass test
  - Acute bacterial prostatitis
    - prostatic fluid purulent, systemic signs of infection, bacteria cultured from prostatic fluid
  - Chronic bacterial prostatitis
    - significant # of pathogenic bacteria recovered from purulent prostatic fluid w/o UTI or significant systemic signs
  - Nonbacterial prostatitis
    - significant numbers of bacteria not cultured from prostatic fluid, but fluid consistently revealed microscopic purulence
  - Prostatodynia
    - remaining patients who had persistent pain and voiding complaints as in the previous two categories but w/o bacteria or purulence in prostatic fluid
- NIH Classification (1995)
  - Category I = *acute bacterial prostatitis*
  - Category II = *chronic bacterial prostatitis*
  - Category III = "presence of GU pain w/o uropathogenic bacteria detected by standard methods"
    - category IIIA → inflammatory CPPS (pain + WBC) = CP/CPPS
      - ◆ based on presence of ++ WBC in EPS or postprostatic massage urine (VB3) / semen
      - ◆ same as previous *nonbacterial prostatitis*
    - category IIIB → noninflammatory CPPS (pain w/o WBC)
      - ◆ no significant WBC in EPS or postprostatic massage urine (VB3) / semen
      - ◆ same as previous *prostatodynia*
  - Category IV (WBC w/o pain)
    - asymptomatic inflammatory prostatitis (AIP)
    - ++ WBC (or bacteria or both) in prostate-specific specimens (EPS, semen, tissue biopsies) w/o typical chronic pain
    - includes inflammation seen in histologic specimens, patients with BPH or prostate cancer, and semen specimens of infertility patients

### What is the clinical presentation of prostatitis?

- Category I—Acute Bacterial Prostatitis
  - acute onset pain, irritative + obstructive voiding symptoms, systemic febrile illness
  - LUTS, retention, strangury
  - perineal and SP pain, pain or discomfort of external genitalia
  - systemic symptoms: F/C, N/V, sepsis, hypotension
  - variable symptoms
- Category II—Chronic Bacterial Prostatitis
  - history of documented recurrent UTIs in 25% to 43% → most important
  - relatively asymptomatic b/w acute episodes
- Category III—Chronic Pelvic Pain Syndrome
  - presenting sx of IIIA and IIIB are identical
  - predominant sx = pain: usually in perineum, SP area, and penis → also in testes, groin, low back, or post-ejaculatory
  - LUTS, occasional ED
- Category IV—Asymptomatic Inflammatory Prostatitis
  - present with BPH, increased PSA, prostate cancer, or infertility
  - microscopy of EPS / semen, histologic examination of prostate shows prostatic inflammation

### How may one assess the symptoms present in prostatitis?

## Chapter 15 Questions - Prostatitis.doc

- **NIH-CPSI:** 9 questions
  - Pain: location, severity, frequency (4 qns)
    - pain/discomfort in the last week in: perineum, testicles, tip of penis, below waist (Y/N)
    - pain or burning in the last week during urination / during or after ejaculation (Y/N)
    - frequency of pain / discomfort over the last week
    - measure 0-10: best description of AVERAGE pain or discomfort over last 1 week
  - Urinary function: irritative and obstructive (2qns)
    - frequency of sensation of incomplete emptying over the last week
    - urinary frequency over the last week
  - QOL and daily activities (3 qns)
    - sx preventing normal activities?
    - preoccupation w/ symptoms over the last week?
    - If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

### What is involved in the evaluation of a pt w/ suspected prostatitis?

- Hx: as above
- Px: usually not helpful
  - Category I (acute bacterial prostatitis): febrile, tachycardic, tachypneic, hypotensive
    - SP or perineal pain, urinary retention
    - DRE: hot, boggy, tender
    - EPS unnecessary, perhaps even harmful
  - Category II or III (CPPS): exam usually unremarkable
- Cytology and cultures
  - Category I: urine culture all that is needed
    - four-glass urine collection technique – 91% sensitivity and specificity
      - ◆ VB1: voided bladder-1- first 10 ml of urine, represents the urethral specimen
      - ◆ VB2: voided bladder-2 - similar to MSU, represents the bladder urine
      - ◆ EPS - collected into sterile container during prostatic massage
      - ◆ VB3: - 1st 10ml urine voided after prostatic massage, includes EPS in prostatic urethra
      - ◆ centrifuge urines X 5min, examine sediment for WBC, macrophages, oval fat bodies, RBC, bact
    - **premessage and postmessage test (2-glass test)** – has replaced time-consuming 4-glass test
      - ◆ VB3 almost as accurate as EPS (92% sensitivity; 99% specificity) for prostate-specific inflammation
  - Category II: 10X increase in bacteria in EPS / VB3 specimen compared w/ VB1 + VB2
    - localization of bacteria in the postprostatic massage urine or EPS is diagnostic
  - Category IIIA: dx w/ no uropathogenic bacteria cultured, but ++WBC (> 5-10 WBC/HPF) in EPS / VB3 / both
  - Category IIIB: dx w/ no uropathogenic bacteria cultured, and no WBC in EPS or VB3 sediment
- Urodynamics
  - reported UDS results in CP pts:
    - 50% had bladder areflexia w/ nonrelaxing perineal floor (striated muscle spasm)
    - 36% had bladder hyperreflexia with appropriate striated sphincter relaxation
    - decreased peak and mean urinary flow rates
    - elevated maximal urethral closing pressure
    - incomplete funneling of BN + urethral narrowing at external sphincter during voiding
  - pts w/ undiagnosed chronic voiding dysfunction often misdiagnosed as CP
    - 54% primary vesical neck obstruction
    - 24% functional obstruction localized to the membranous urethra (pseudodyssynergia)
    - 17% impaired bladder contractility
    - 5% acontractile bladder
    - 49% detrusor instability
- Endoscopy
  - cysto not usually indicated
  - indicated if possibility of dx other than CP/CPPS:
    - Hx: hematuria
    - Lower urinary tract evaluation: VB1 urinalysis, UDS
- Transrectal Ultrasonography
  - no significant differences in U/S patterns of pts w/ nonbacterial prostatitis and controls
    - can diagnose cysts, diagnosing and draining prostatic abscess or seminal vesicles
- Prostate Biopsy
  - importance and interpretation unclear → research tool only

## Chapter 15 Questions - Prostatitis.doc

- pathogenic bacteria seen on bx in pts w/ hx CBP with sterile EPS cultures after antibiotics
- Other
  - Ab to G-ve bacterial Ag – only seen in bacterial prostatitis pts
    - Ab +ve pts don't respond to antibiotics better than Ab -ve
  - IL-1 $\beta$  and TNF- $\alpha$  – increased in Type III compared to controls
    - IL-1 $\beta$  and IL-8 higher in IIIA patients than in IIIB, but no difference in TNF- $\alpha$ , IL-1 $\alpha$ , or IL-6
    - IL-1 $\beta$  in EPS higher in men w/ IIIA and IIIB compared to controls
    - direct relx b/w # WBC in EPS and IL-1 $\beta$  levels in EPS
  - Zn – not helpful

### What are the most common organisms found in EPS?

- Enterobacteriaceae (ex: *E. coli*, *Serratia*, *Klebsiella*, *Proteus*, *Pseudomonas*) most common
- urethral G+ve (*S. epidermidis*, *S. saprophyticus*, *Corynebacterium*, *Bacteroides*)

### How does one differentiate b/w IIIA and IIIB CPPS?

- depends on cytologic examination of urine / EPS / both
  - no validated cut-off point for WBC/HPF to disting. inflammatory from noninflammatory CPPS
    - usually 2-20, most ppl take 10 WBC/HPF in EPS as upper level of normal
  - cells may clump or aggregate → makes quantifying them impossible
  - unstained specimen → can't differentiate type of white blood cell
  - can use glass hemacytometer (cls/mm<sup>2</sup>) → more accurate
  - semen examination increases % of pts identified as IIIA CPPS

### What are the proposed causes for persistent urinary symptoms in prostatitis?

- detrusor vesical neck or external sphincter dyssynergia
- proximal or distal urethral obstruction
- fibrosis or hypertrophy of vesical neck

### What are the reported features of prostatitis on TRUS?

- inhomogeneous echo structures
- constant dilatation of periprostatic venous plexus
- elongated seminal vesicles
- thickening of the inner septa

### What are the treatment options for prostatitis?

- Antimicrobials
  - bacteria cultured in only 5%, but may be cause in more cases
  - acid antibiotics in prostatic secretions only in very low concentrations → alkaline much higher
  - drug penetration dependent on lipid solubility, degree of ionization, degree of protein binding, and size and shape of antimicrobial molecule
    - TMP concentrates in prostate and plasma levels, SMX and amp do not
    - fluoroquinolones don't concentrate in prostate 2<sup>o</sup> to lipid solubility and protein-binding
  - Acute Bacterial Prostatitis
    - start w/ IV antibiotics, change to PO
      - ◆ IV amp+gent or cephalosporin or quinolone, change to PO TMP/SMX or quinolone
      - ◆ optimal duration not known: 2-4 weeks OK
  - Chronic Bacterial Prostatitis
    - eradication of pathogens in CP w/ TMP/SMX ranges from 0-67%; longer duration (90 days) gives best results
    - fluoroquinolones: improved results in CP 2<sup>o</sup> to *E. coli* and other Enterobacteriaceae
      - ◆ not in prostatitis from *Pseudomonas* or enterococci
      - ◆ 1mo quinolone better than 3mo Septra if *E. coli* CP
  - Type III: no study comparing antibiotics to placebo
    - should not be given beyond 6-8wks w/o appraisal of its effectiveness
- $\alpha$ -Blocker Therapy
  - CP/CPPS pts have ++ LUTS, related to poor relaxation of BN during voiding
  - “dysfunctional” voiding may cause reflux of urine into prostatic ducts → inflammation + pain
  - alpha blockade may improve obstruction, improving flow + decreasing ductal reflux
  - diphenoxybenzamine / phenoxybenzamine vs. placebo: symptomatic improvement, but ++ s/e
  - alfuzosin vs. placebo: improvement in max flow rate and symptom scores, s/e OK
  - terazosin: 76% had sx improvement after 1mo, 58% asymptomatic off therapy 2mo later

## Chapter 15 Questions - Prostatitis.doc

- 42% required reinitiation of therapy to relieve recurrent symptoms
- ➔  $\alpha$ -blocker + antibiotics vs. antibiotics alone: sx of CBP better w/ combination
- ➔ **no large-scale phase III trials available for efficacy of  $\alpha$  blockers vs. placebo**
- Anti-inflammatory Agents and Immune Modulators
  - ➔ inflammation and elevated semen cytokines seen in CP/CPPS
  - ➔ NSAID quickly relieves dysuria (relieved in 66%), strangury, and painful ejaculation
  - ➔ pentosan polysulfate (as in IC): pain and QOL improved in 40%
- Muscle Relaxants
  - ➔ ? sx 2° to sm/skel neuromuscular dysregulatory phenomenon in perineum / pelvic floor
  - ➔  **$\alpha$  blockers + skel.muscle relaxants + medical/physical therapies advocated and promoted**
  - ➔ crossover trial of phenoxybenzamine, baclofen, placebo each x 1mo in IIIB pts:
    - improvement in 37% of pts w/ baclofen, 8% w/ placebo
- Hormone Therapy
  - ➔ antiandrogens (5- $\alpha$ -reductase inhibitors) may cause:
    - regression of prostatic glandular tissue
    - improved voiding parameters (especially in older patients with BPH and prostatitis)
    - reduced intraprostatic ductal reflux
  - ➔ placebo vs. finasteride in Type III: finasteride reduced prostatitis and BPH sx scores
    - no statistically significant difference in pain, but not a very good study
- Phytotherapeutic Agents
  - ➔ plant extracts may have 5- $\alpha$ -reductase activity,  $\alpha$ -adrenergic blockade activity, effects on bladder contractility, and anti-inflammatory properties
  - ➔ Cernilton (bee pollen extract): 50% improvement in pain and irritative voiding symptoms
  - ➔ Quercetin (bioflavonoid): 67% treated (vs. 20% placebo) had >25% reduction in sx
- Allopurinol
  - ➔ intraprostatic ductal reflux of urine increases conc of metabolites w/ purine and pyrimidine bases in the prostatic ducts, causing inflammation
  - ➔ clinical trials: no significant improvement
- Physical Therapy
  - ➔ Prostatic Massage
    - may drain theoretically occluded prostatic ducts, improving circulation and antibiotic penetration
    - uncontrolled studies show some benefit with repetitive prostatic massage x 4-6wks (w/ abx)
  - ➔ Perineal or Pelvic Floor Massage and Myofascial Trigger Point Release
    - potential treatments: heat therapy, PT massage, ischemic compression, stretching, anesthetic injections, acupuncture, electroneural modulation, relaxation exercises, yoga, hypnosis
  - ➔ Biofeedback
    - ? pain 2° to pseudodyssynergia during voiding or repetitive perineal muscle spasm
    - small uncontrolled studies: biofeedback does help specific prostatitis-like symptoms
- Minimally Invasive Therapies
  - ➔ Balloon Dilatation: not been routinely employed in clinical practice
  - ➔ Minimally Invasive Surgery: TUNA
  - ➔ Microwave Hyperthermia and Thermotherapy
    - microwave vs. sham: 75% vs. 52% improvement in sx
    - **restricted to patients with refractory or end-stage symptoms**
- Surgery
  - ➔ Category I: urinary obstrx common
    - SP tube better than Foley, as doesn't further obstruct ducts
    - CIC or short-term Foley OK
  - ➔ prostate abscess: dx w/ TRUS or CT if don't respond quickly to antibiotics
    - drain by transurethral incision, or transperineal if penetrated beyond capsule or levator ani
  - ➔ SV abscess: dx traditionally w/ seminal vesiculography, now w/ CT or MR
    - tx: antibiotics, transrectal aspiration, removal of SV
  - ➔ **surgery usually doesn't have role in CP treatment, unless specific indication (ex: stricture, BN obstruction)**
  - ➔ no substantial proof in the literature as to the efficacy of major prostate surgery in category II CP
    - transurethral resection of the prostate has not been advocated for category III CPPS
  - ➔ **surgery should not be encouraged or recommended at this time**

### What are the mechanisms of action of antibiotics in CPPS?

- strong placebo effect
- eradication or suppression of noncultured microorganisms

## Chapter 15 Questions - Prostatitis.doc

- independent anti-inflammatory effect of some antibiotics

### What are the potential etiologies of myofascial trigger points in the perineum or pelvis?

- mechanical abnormalities in the hip and lower extremities
- chronic urinary holding patterns (dysfunctional toilet training)
- sexual abuse
- repetitive minor trauma
- constipation
- unusual sexual activity
- recurrent infections or surgery
- stress and anxiety

### By what proposed mechanisms does microwave therapy improve sx in prostatitis?

- accelerates process of fibrosis or scar formation in the area of chronic inflammation
- alters afferent nerve fibers for pain
- kills nonculturable bacteria

### Describe the clinical algorithm that should be used in pts w/ prostatitis.

- Medications
  - Antibiotics
    - SMX-TMP DS 2 tab BID x 12wks
    - Norfloxacin 400mg BID x 4-12wks
    - Ciprofloxacin 500mg BID x 4-12wks
    - Ofloxacin 300mg BID x 4-12wks
    - Lomefloxacin 400mg qd x 4-12wks
  - $\alpha$  Blockers
    - Phenoxybenzamine 10mg BID x 12wks
    - Alfuzosin 2.5mg TID x 6wks
    - Terazosin 5mg qd x 4-52wks
  - Phytotherapy
    - Pollen extract
    - Quercetin
  - Anti-inflammatory
    - Nimesulide
    - Other NSAIDs
    - Indomethacin
    - Diclofenac
    - Ibuprofen
    - Rofecoxib 25–50 mg qd x 6wks
    - Pentosan polysulfate 100mg TID x 24wks
  - Finasteride 5mg qd x 24wks
  - Allopurinol 300-600mg qd x 24-30wks
- Category I
  - antibiotics +/- drainage, **keep high suspicion for prostatic abscess**
- Category II
  - rare: respond to quinolone x 4-12wks
  - antibiotics x 4-12wks → antibiotics + massage → suppressive antibiotics → surgery (last resort)
  - low-dose prophylactic or suppressive antimicrobial agents for recurrent or refractory prostatitis
    - addition of repetitive prostatic massage may have further added benefit
- Category III
  - IIIA
    - antibiotics → massage → alpha blockers → anti-inflammatories → phytotherapy → finasteride → surgery (if indicated) → microwave (last resort)
  - IIIB
    - analgesics, anti-inflammatories, +/- muscle relaxants, alpha blockers, benzos → PT (biofeedback, massage, trigger pts) → surgery → reassurance and psychological support
  - perform lower urinary tract evaluation (two-glass premassage and postmassage screen)
  - microscopy of postprostatic massage urine sediment to differentiate inflammatory from noninflammatory CPPS
  - use newly validated NIH-CPSI
  - trial of antibiotic therapy that would cover *Chlamydia* and *Ureaplasma*

### **Chapter 15 Questions - Prostatitis.doc**

- $\alpha$ -blocker therapy (esp if obstructive voiding symptoms); anti-inflammatory agents; muscle relaxants and consideration of finasteride, phytotherapy, pentosan polysulfate (esp if IC-type sx), and specific physical therapy
- Category IV
  - does not require symptomatic therapy
  - antibiotics may be indicated if booked to undergo endoscopic procedures, or if increased PSA or infertility



## **Chapter 16**

### **• Interstitial Cystitis and Related Disorders •**

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#### **What is IC?**

- incurable condition characterized by chronic pelvic pain and urinary frequency in the absence of any known etiology

#### **What is the difference b/w IC and PBS (painful bladder syndrome)?**

- PBS = SP pain related to bladder filling, accompanied by sx like increased frequency in the absence of UTI or other pathology
- IC = same as above, + typical cystoscopic and histologic features

#### **What are the sx of IC?**

- allodynic sx (exaggeration of normal sensx)
- bladder and/or urethral and/or pelvic pain
- irritative voiding sx
  - frequency, urgency
- sterile urine cultures
- sx characterized by flares and remissions
  - long-term severity is stable regardless of tx

#### **What are the NIDDK diagnostic criteria?**

- National Institute of Diabetes and Digestive and Kidney Diseases workshop in 1987
- meant initially to serve only as a research definition
  - must have glomerulations on cysto or Hunner's ulcer
    - after EUA to 80-100cm H<sub>2</sub>O for 1-2 min
    - must be diffuse, must be 10 glomerulations / quadrant
  - must have pain associated w/ bladder or urgency
- exclusion criteria
  - capacity > 350cc
  - absence of intense urge w/ bladder filled to 100cc gas or 150cc water
  - involuntary contractions
  - sx < 9mo
  - no nocturia
  - sx relieved by antibiotics, antiseptics, anticholinergics, or antispasmodics
  - frequency < 8x / day
  - dx of bacterial cystitis or prostatitis w/i past 3mo
  - bladder/ureteral calculi
  - active HSV
  - cancer: uterine, cervical, vaginal, urethral
  - urethral diverticulum
  - cyclophosphamide/chemical cystitis
  - TB cystitis
  - radiation cystitis
  - vaginitis
  - <18yrs

#### **What are the ICDB eligibility criteria?**

- Interstitial Cystitis Data Base research criteria
  - >18yrs
  - urgency, frequency, pain > 6mo
  - frequency (voiding > 7x / day) or urgency
  - no hx GU TB



## Chapter 16 Questions - IC.doc

- no hx urethral ca
- no hx TCC
- no hx prostate ca
- no hx ovarian, vaginal, or cervical ca
- no UTI
- no HSV
- no antibiotics for UTI x 3mo
- no hx cyclophosphamide
- no radiation cystitis
- no neurogenic bladder
- no BOO determined by UDS
- no prostatitis x 6mo
- no stones x 3mo
- no urethritis x 3mo
- no hx urethral dilx, CMG, cysto under GA, bladder bx x 3mo
- no hx augment, cystectomy, cystolysis, neuroectomy
- no stricture < 12F

### Describe the natural hx of IC.

- from Urban Institute and U Penn study (1990)
  - median age 40yrs
  - late deterioration of sx unusual
  - 50% spontaneous remission (mean 8mo)

### What subgroups of pts are more likely to have IC?

- hx of childhood bladder problems
- hx of UTI
- Jewish
- comorbid conditions: depression, chronic pain, anxiety

### What diseases are associated w/ IC?

- allergies/allergic sx → most common (40-45%)
- IBS (30%)
- fibromyalgia
- SLE
- IBD (>7%)
- focal vulvitis
- Sjögren's syndrome

### What are the sx of vulvar vestibulitis syndrome?

- severe pain on vestibular touch to attempt vaginal entry
- tenderness to pressure localized w/i the vulvar vestibule
- physical findings confined to vulvar erythema

### What are the sx of Sjogren's syndrome?

- autoimmune exocrinopathy w/ F preponderance
  - dry eyes, dry mouth, arthritis
  - fever
  - GI/pulmonary sx

### What are the potential etiologies of IC?

- **Mnemonic - MAN'S IUD**
  - Mast cell involvement
  - Autoimmunity/inflammation → no clear role
  - Neurogenic mechanisms: may be related to activation of mast cells
  - Stress → no data to show stress initiates IC, but can increase sx severity
  - Infection → little data to support this
  - Urine abnormalities: APF may be the cause
  - Defect in GAG layer + epithelial permeability: population of IC pts w/ increased permeability
  - hypoxia and RSD → no evidence

## Chapter 16 Questions - IC.doc

→ estrogen → more bladder mast cells w/ high-affinity estrogen R in IC pts

### What animal model represents the animal equivalent of IC?

- feline urologic syndrome

### What is the role of mast cells in IC?

- **increase in urothelial mast cells** → part of generalized inflammatory cell reaction regardless of etiology
  - produce histamine: causes pain, hyperemia, and fibrosis (all present in IC)
- secondary population of mast cells in the lamina and epithelium → distinct from those in the detrusor
- mast cells more active in ulcerative form of IC
- mast cells more likely to be degranulated or active than in other conditions
  - may be due to final common pathway from multiple causes

### What are the proposed mechanisms by which mast cells can contribute to the failure of epithelialization of the bladder after injury?

- inhibition of epithelial cell replication
- interference w/ epithelial cell spreading

### What are the major classes of GAGs?

- hyaluronic acid (HA)
- heparin sulfate
- chondroitin 4-sulfate
- keratan sulfate

### What is the role of the GAG layer in the bladder?

- permeability and antiadherence barrier
  - IC pts may have a defect in the epithelial permeability barrier of the bladder surface GAGs
  - lower excretion of urinary uronic acid and GAGs in IC pts
  - deficit of bladder luminal and basal proteoglycans

### What is the KCl sensitivity test?

- water vs. 0.4M KCl placed into bladders of normal pts and IC pts
  - water did not provoke sx in either group
  - KCl provoked 4.5% controls and 70% of IC pts
  - sx reduced in pts on heparinoid therapy

### How do neurogenic mechanisms cause inflammation in the bladder?

- activation of sensory nerves (pain fibres) triggers neurogenic inflammation through release of neuropeptides
  - substance P, neurokinin A, and CGRP
- increases tissue edema, vascularity, w/ leukocyte adhesion, mast cell degranulation
- increased sympathetic activity in IC

### How does the CNS contribute to the chronic nature of IC?

- "wind-up" phenomenon
  - repetitious stimulation of a peripheral nerve at sufficient intensity to activate C fibers results in progressive buildup of the magnitude of the electrical response recorded in the 2<sup>nd</sup>-order dorsal horn neurons
  - dependent on NMDA receptors in the spinal cord
  - causes "pain memory"

### What are the characteristic clinical features of non-nociceptive pain?

- description of the pain inappropriate in comparison to pathology (which may be normal)
- hyperalgesia: noxious stimuli cause pain out of proportion to what would be expected
- allodynia: non-noxious stimuli cause pain
- extent of pain boundary greater than expected on basis of site of original pathology

### What is the pathology that exists in RSD?

- **abnormal synaptic activity b/w sensory afferent and sympathetic efferent neurons**
  - excessive sympathetic outflow leads to constriction of blood vessels and tissue ischemia
  - sets up further changes and perpetuates the cycle
- trigger event usually leads to changes in RSD: ? inflammatory response to injury: UTI

## Chapter 16 Questions - IC.doc

- no studies have shown that any case of IC is related to RSD

### What urine abnormalities may exist in IC?

- component of urine may access the interstices of the bladder wall → inflammatory response  
→ IC urine causes higher cell death to cultured transitional cells: ? toxic compound
- antiproliferative factor (APF) in the urine of IC pts identified  
→ made or activated in bladder or distal ureter  
→ inhibits normal bladder epithelial regeneration
- failure of substitution cystoplasty and continent diversions  
→ pain or contraction of bowel segment over time

### What are the different possibilities for autoimmunity involvement in IC?

- direct autoimmune attack
- indirectly as a result of tissue destruction and inflammation from other causes
- autoimmune phenomena unrelated to disease

### What microscopic picture is pathognomonic of IC?

- none: pathologic findings not consistent  
→ transition from nonulcerative to ulcerative IC is a rare event: may be 2 separate entities

### What is the role of bx in diagnosing IC?

- bx often not helpful  
→ even severely abnormal microscopic picture does not indicate a poor prognosis

### Describe the initial evaluation of IC.

- Hx
  - pain, urgency, frequency, pressure, dysuria
    - location of pain: usually dyspareunia, may be SP, perineal
    - pts often limit fluid intake
    - urgency: depends on definition
  - ejaculatory pain
  - hematuria
  - dysphoric mood
  - voiding diary
    - why does pt void hourly?: pain vs. convenience
  - meds
    - cyclophosphamide, ASA, NSAIDs, allopurinol: cause nonbacterial cystitis that resolves
  - must r/o other disorders
    - hx of UTI, ca, cystitis, malakoplakia, schistosomiasis, scleroderma, endometriosis
    - chemo, rads, no sx w/ antibiotics, OAB, vaginitis, HSV, vulvodynia, vulvovestibulitis, urethral diverticulum
    - bacterial cystitis, urethritis, prostatitis, STD
  - questionnaires
    - PUF: pain, urgency, frequency
- Px
  - most common area of pain: BN tenderness (Teichmann, 2004)
  - SP tenderness
- Labs
  - cultures, U/A, cytology
- Radiology
  - IVP, cysto
- cystoscopy
  - local: **pain on bladder filling w/ reproduces pts symptoms is very suggestive of IC**
- if sx do not resolve, or do not respond to tx
  - education, behavioural modification, self-empowerment, dietary changes, nonprescription analgesia
- if sx not tolerable
  - PO medications for IC
  - EUA w/ hydrodistension
    - glomerulations not specific
  - bladder bx only to r/o other lesions
  - UDS

## Chapter 16 Questions - IC.doc

- can demonstrate normal compliance and reproduce sx during filling, can r/o bladder instability
- UDS: BN obstruction, pseudodyssynergia, impaired contractility

### What are the potential causes for glomerulations on hydrodistension?

- radiation
- carcinoma
- toxic chemicals or chemo
- dialysis
- diversion
- prostate pain syndromes

### What are the potential IC markers that have been investigated?

- mast cell
- eosinophilic cationic protein
- GAG excretion
- urinary histamine and methylhistamine
- "urine antiproliferative factor" (APF)
  - unique protein found only in urine of IC pts
  - made or secreted by distal ureter

### Describe the initial therapeutic approach to IC.

- hydrodistension of the bladder
  - cysto
  - washings for cytology
  - distend bladder x 1-2min at 80cm H<sub>2</sub>O
  - bladder emptied and refilled to look for glomerulations
  - 2<sup>nd</sup> distension for 8 minutes
  - biopsy after 2<sup>nd</sup> distension if needed
  - average duration of relief of sx: 2 months, modest relief if at all
  - bladder can be thin: possibility of perf/rupture
  - **capacity of < 200cc under anaesthesia = poor results**
- pt education and empowerment: on-line databases, interactive computer programs, hotlines, videos
- reassure pt
- voiding diary
- exercise, decrease stress, take warm baths, biofeedback, massage
- dietary changes as needed: avoid caffeine, EtOH, cranberry juice

### What are the determinants of success for medical tx of IC?

- bladder capacity
  - capacity under anaesthesia < 200cc poor chance of success

### What medical treatments are available for the tx of IC?

- historical agents: don't work
  - hormones, vitamin E, anticholinergics, antispasmodics
  - immunosuppression, chloroquine, cyclosporine
  - opiate antagonist: nalmifene
  - CCB: nifedipine
  - L-arginine
- TCA: staple of PO treatment
  - amitriptyline 25-150mg OD
    - only 1 RCT (2004): significant improvement vs. placebo
- antihistamines
  - hydroxyzine (Atarax) 25mg PO qhs
    - potential allergic etiology, increased mast cells
    - H<sub>1</sub> receptor antagonist, anxiolytic, anticholinergic
- sodium pentosanpolysulfate (PPS) = Elmiron
  - heparin analogue in PO formulation: 3-6% excreted into urine
    - relief of pain: complete in 35%, partial in 23%
  - requires 3-6mo treatment trial for sx improvement
  - hydroxyzine vs. PPS: neither helped any pts

## Chapter 16 Questions - IC.doc

- useful for radiation cystitis
- titrate down to decrease dose after remission
- analgesics
  - non-opioids: acetaminophen, NSAIDs → can reach a ceiling for maximum analgesic effect
  - gabapentin 300-2100mg
    - very little in literature to support use
  - opioids: long term use in the rare pt that has failed all other forms of conservative therapy

### What are the major pharmacologic actions of TCAs?

- central and peripheral anticholinergic actions
- block active transport of NE and 5-HT<sub>2</sub> in the presynaptic nerve ending (SNRI)
  - desensitize  $\alpha_2$  receptors on central noradrenergic neurons
- sedative effect: may be related to antihistaminic properties

### What are the contraindications for TCAs?

- long QT syndrome or significant conduction system disease
- after recent MI (within 6mo)
- unstable angina
- CHF
- frequent PVC
- hx of sustained SVT
- orthostatic hypotension
- suicidality

### What intravesical treatments have been used for the tx of IC?

- silver nitrate: 30-60cc of 1:5000 solution of silver nitrate for 3-4min, repeated q2d
  - dysuria and vesical irritability for 2-3hrs
  - 14% cure, 79% improved
  - contraindication: VUR
- chlorpactin WCS-90 0.2% (modified derivative of hypochlorous acid in a buffered base)
  - complication: ureteral fibrosis
  - contraindication: VUR → must do VCUG
- DMSO (Rimso) 50cc of 50% solution for 15min
  - product of the wood pulp industry, derivative of lignin: solvent properties
  - weekly x 6
  - **no s/e other than garlic breath**
  - works in 50-90% for 1-3mo
  - very few studies
    - one RCT (1991): q2 weekly installation, 53% improvement vs. 18% control
- heparin 10000-40000u 2x weekly
  - can mimic the activity of the bladder's MPS lining
  - anti-inflammatory effects, inhibition of fibroblast proliferation, angiogenesis, and smooth muscle cell proliferation
  - virtually no systemic absorption, even in cystitis
  - short FU, no controls
- PPS 300mg in 50cc NS twice weekly
  - modest benefit
- HA (Cystistat): 40mg in 40cc NS weekly x 6
  - 30-90% improvement, small #'s, no controlled studies
  - \$200 per treatment
- chondroitin sulfate (Uracyst)
  - 20ml 0.2% weekly x 4, then monthly x 12
  - only 30% response rate
- doxorubicin
- cromolyn sodium
- BCG
  - BCG vs. placebo: 60% vs. 27% relief in placebo, durable to 2 yrs
    - didn't worsen any sx
  - BCG vs. DMSO: similar efficacy
- oxybutynin
- EMDA w/ lidocaine and dexamethasone

## Chapter 16 Questions - IC.doc

- capsaicin/resiniferatoxin
  - pilot studies only: no benefit in early results

### What non-medical treatment is available for IC?

- nerve stimulation
  - TENS: electrodes 10-15 cm apart immediately above pubis
    - 2-50Hz frequency used x 30-120min
    - pain improves more than frequency
    - relieves sx by stimulating myelinated afferents to activate segmental inhibitory circuits
  - acupuncture
  - neuromodulation
- surgery: only after all trials of conservative treatment have failed in motivated and well informed pt that has severe unresponsive disease
  - denervation procedures: all failed
    - sympathectomy, intraspinal EtOH injections, transvesical infiltration of pelvic plexus w/ phenol: failure
  - TUR/laser of Hunner's ulcer: some sx relief
    - no justification for using laser to treat glomerulations
  - supratrigonal cystectomy
    - **may need CIC post-op → disaster for IC pt!!**
  - augmentation cystoplasty
  - diversion w/o cystectomy
  - cystectomy and diversion: indicated in pts who are miserable, and have failed all other therapies, and have poor likelihood of remission
    - conduit
    - neobladder

### What complications can befall the IC bladder after a diversion w/o cystectomy?

- pyocystitis
- hemorrhage
- severe pain
- sensation of incomplete emptying
- bladder ca

### Describe the treatment progression for pts w/ IC.

- employ one treatment at a time
- **pt education**
  - most important step
  - lifestyle modification: diet, behaviour
- oral therapy
  - non-narcotics, antispasmodics, amitriptyline x 8 weeks
  - hydroxyzine x 8 weeks if fails
  - PPS x 6-9 mo if fails
- fulgurize Hunner's ulcers if present
- EUA and bladder hydrodistension
- intravesical therapy
  - DMSO x 6 weekly installations +/- steroid, bicarb, heparin
    - mix 50ml DMSO w/ 10000u heparin, 10mg triamcinolone, 44mEq bicarb
  - intravesical heparin
  - intravesical chlorpactin
- other therapies
  - pain clinic referral
  - experimental
  - neuromodulation, TENS
  - diversion +/- cystectomy

### What is the urethral syndrome?

- nonspecific group of sx including frequency, urgency, dysuria, SP pain w/o any objective findings → term is no longer used

### What is CPPWOP?

## **Chapter 16 Questions - IC.doc**

- chronic pelvic pain w/o obvious pathology
  - chronic pelvic pain that appears gyne, but no lesion seen
  - lap dx of exclusion

### **How can one classify pelvic pain syndromes?**

- poorly characterized conditions
  - GU: scrotal pain, PBS/IC, prostate pain, penile pain, urethral pain
  - gyne: endometrial pain, vulvar pain syndrome, vaginal pain syndrome
  - anorectal: proctalgia fugax, anorectal, anismus
  - MSk: perineal, pelvic floor
  - neurologic: pudendal pain syndrome
- well characterized conditions
  - GU: IC, prostatitis, urethritis, epididymo-orchitis
  - gyne: endometriosis
    - probably causes pain
    - only 1 double-blinded study showed lysis of adhesions resulted in improvement in sx
  - anorectal: proctitis, hemorrhoids, anal fissure
  - neurologic: pudendal neuropathy, sacral cord pathology

### **What is the relationship of pelvic adhesions to pelvic pain?**

- uncertain and controversial
  - presence of adhesions is not a reliable predictor of pelvic pain
  - difficult to demonstrate relationship b/w duration and severity of pain and extent or location of adhesions

### **What is viscerosomatic convergence?**

- makes subjective discrimination of somatic and visceral pain difficult
- occurs at level of dorsal horn of cord
- peripheral somatic and visceral nerves synapse at same transmission cell which sends pain signal to brain
- pt cannot distinguish visceral from abdominal pain

### **What are the indications for gyne workup for IC/PBS?**

- pain is predominant complaint, rather than frequency and pain



## **Chapter 17**

### **• Sexually Transmitted Diseases •**

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#### **What groups are at higher risk of contracting an STD?**

- men
- low socioeconomic class
- blacks
- drug users
- urban
- adolescent

#### **Why are men more often diagnosed w/ an STD?**

- sx and signs more obvious
- **more sexual partners**

#### **Which STDs require contact tracing and treatment of sexual partners?**

- syphilis
- gonorrhoeae
- chlamydia

#### **What is the incubation period for gonococcal urethritis?**

- 3-10 days
- exceptions are very common: can vary from 12hrs to 3 months  
→ most commonly reported communicable disease in the US

#### **What is the risk of getting gonorrhoeae from a single episode of intercourse w/ an infected partner?**

- men: 17%

#### **What are the sx of gonorrhoeae?**

- profuse urethral discharge: may be scant or even absent
- dysuria
- asymptomatic in 40-60%
- improves even without tx, but host remains a carrier

#### **How can one make a dx of gonorrhoeae?**

- urethral swab: must be inside urethra 2-4cm, not from urethral discharge  
→ Gram stain  
→ plate directly onto Thayer-Martin and New York City medium  
→ DNA probe tests

#### **What is the treatment for gonorrhoeae?**

- drug of choice: ceftriaxone 125mg IM x 1 plus either azithromycin 1g PO x 1 or doxycycline 100mg PO BID (for chlamydia)
- alternates  
→ cefixime 400mg PO / cipro 500mg PO / ofloxacin 500mg PO plus either azithro or doxy

#### **Why does the treatment of gonorrhoeae include doxy or azithromycin?**

- 30% of men w/ GU also have chlamydia

#### **What is the etiology of non-gonococcal urethritis (NGU)?**

- *Chlamydia trachomatis*: 30-50%
- *Ureaplasma urealyticum*: 20-50%
- unknown: 20-30%



## Chapter 17 Questions - STDs.doc

- *Mycoplasma genitalium* and *Trichomonas vaginalis* have been implicated
- urethritis in homosexual men more likely to be gonococcal

### What are the RF for developing NGU?

- RF for all STDs
- smoking
- genital-oral intercourse

### What is the incubation period for NGU?

- 1-5 weeks

### What are the sx for NGU?

- scant urethral discharge, but may be thick and purulent
- urethral itch may be the only sx
- asymptomatic in 40-60%, esp in contacts of women w/ cervical infection w/ chlamydia

### How does one diagnose NGU?

- urethral swab (wait 4 hrs after voiding)
  - Gram stain: >4 PMN per HPF
- first-void urine
  - spun sediment: >15 PMN per HPF
  - WBC on dipstick
- *Chlamydia* cultures: from urethral swab, not from exudate
- other assays
  - direct fluorescent antibody (DFA)
    - *Chlamydia*-specific monoclonal Ab conjugated to fluorescent stain
  - ELISA
  - nucleic acid probes

### What is the treatment for NGU?

- treat all partners
  - azithromycin 1g PO x 1 or doxycycline 100mg PO BID x 7d
  - alternate: erythromycin 500mg PO QID or ofloxacin 300mg PO BID x 7d

### What is the natural hx of NGU post-treatment?

- clear or mucoid discharge after therapy – may last for days-weeks
- persistent urethral itch or dysuria not uncommon

### What are the causes for recurrent NGU?

- reinfection w/ original organism (from non-treated sexual partner)
- resistance
  - usually due to tetracycline-resistant *Ureaplasma urealyticum* → treat w/ erythromycin x 1-2weeks
  - *Chlamydia* is usually not resistant to tetracyclines

### What is the evaluation for men w/ recurrent or persistent urethritis despite treatment for GU/NGU?

- urethral swabs: *Neisseria gonorrhoeae* and *Chlamydia trachomatis*
  - false –ve if perform too soon: wait > 48h for gonorrhoeae or 3 weeks for Chlamydia
  - re-treat w/ erythromycin base 500mg PO QID for 2 weeks if cultures –ve
  - if fails 2<sup>nd</sup> course, no need to get 3<sup>rd</sup> set of cultures
- cultures for fungus
- examine sexual partner
- uroflow and cysto: detect possible intraurethral lesions

### What are the complications of NGU in men?

- usually none
- guilt?

### What are the complications of NGU in women?

- PID → 40% of PID in the US is caused by *C. trachomatis*
- infertility → due to tubal occlusion from scarring
  - chance of sterility from single episode of NGU: 12%

## Chapter 17 Questions - STDs.doc

- 2 episodes: 35%
- 3 episodes: 75%
- ectopic pregnancy: most common cause of ectopic is tubal damage from PID
- chronic abdo pain: in 15% of women w/ hx of PID
- perinatal infections

### What are the chances of perinatal infection of NGU during vaginal delivery?

- 15% develop chlamydial pneumonia
- 50% develop chlamydial conjunctivitis

### What are the complications of acute epididymitis?

- abscess formation
- testicular infarction
- chronic pain
- infertility

### What is the etiology of epididymitis?

- Infectious
  - GC or *Chlamydia* in 2/3 sexually active men < 35yrs
  - *E. Coli* if > 35yrs or in children
  - TB
  - *Cryptococcus*
  - *Brucella* } more common in immunosuppressed pplx
- Non-infectious
  - amiodarone: selectively concentrated in the epididymis

### How does one differentiate epididymitis from torsion (i.e. management of the acute scrotum)?

- History and physical
- Labs: Gram stain and culture of urethral swab, urine C&S
- Radiology
  - US scrotum: 1% cord block may help w/ procedure: can press probe against testicle firmly
  - radionuclide scan
  - color duplex Doppler US: sens 82%, specificity 100%
  - MRI

### What is the most accurate method for diagnosing torsion?

- radionuclide scan

### What is the treatment for acute epididymitis?

- urethritis/STD
  - urine C&S
  - single dose tx for GU, 10d course for NGU
  - bed rest and scrotal elevation
  - treat partners
  - syphilis/HIV testing
- bacteriuria cause
  - Gram stain and urethral smear
  - 14d course abx: TMP-SMX, quinolone
  - hospitalization if very ill for IV abx
  - bed rest and scrotal elevation
  - injection of cord w/ anaesthetic
  - NSAIDs
  - evaluate for GU abnormalities if younger boys and older men

### In what instances are the presentations of an ulcer pathognomonic?

- fixed drug eruption: always triggered by the ingestion of one particular medication
- herpes simplex: vesicles on an erythematous base
- trauma: genital ulcer that develops acutely during sexual activity

### What is the DDx for genital ulcers?

## Chapter 17 Questions - STDs.doc

- Premalignant
  - erythroplasia of Queyrat
- Malignant
  - SCC
- Non-malignant
  - syphilis
  - chancroid
  - herpes
  - lymphogranuloma venereum
  - granuloma inguinale
  - fixed drug eruptions
  - traumatic ulcers

### What test is most valuable for each of the following lesions?

- malignant lesion: biopsy
- genital herpes: viral culture
- syphilis: serology and darkfield exam
- chancroid: selective medium culture for *H. ducreyi*
- granuloma inguinale: crush prep for cytologic or histologic identification of *Calymmatobacterium granulomatis*
- lymphogranuloma venereum: PCR, serologic test, culture for *C. trachomatis*

### What is the etiologic agent for genital herpes?

- HSV type 2 in majority
- HSV type 1 usually for oral infections, but reported in 10-25% of cases

### What are the sx of genital herpes?

- dysuria
- neurologic complications: more common in primary infections
  - meningitis w/ spinal fluid leukocytosis
  - urinary retention: sacral or autonomic nervous system dysfunction vs. local pain
  - constipation, weakness, ED, sensory loss
- proctitis: HSV 2<sup>nd</sup> most common cause in gay men, after GC
- extragenital skin lesions: usually from autoinoculation: 10% men, 25% women
- sx usually more severe in women, more severe in 1<sup>st</sup> episode

### How can one diagnose HSV?

- pathognomonic vesicles on erythematous base
- Pap smear: intranuclear inclusions
- immunofluorescent techniques
- viral isolation by culture: most sensitive
- PCR for HSV

### What is the treatment for HSV?

- acyclovir 200mg PO q5h x 7d or 400mg PO TID x 7d
  - acts on viral thymidine kinase as a guanine analogue: inhibits viral DNA polymerase, and also as a chain terminator
  - decreases duration of viral shedding, time to healing, duration of pain
  - suppression dose: 400mg PO BID: consider for pts w/ > 6-8 episodes per year
  - some resistance has occurred
- famcyclovir 250mg PO TID x 7-10d
- valacyclovir 1g PO BID x 7-10d
  - suppression: 1g PO OD
- prophyllactic acyclovir 200mg PO decreases recurrences

### What is the etiologic agent for syphilis?

- *Treponema pallidum* → spirochete

### How does syphilis present?

- 2-4 weeks post-exposure, male pt presents w/ painless penile sore called **chancre**

### What are the different stages of syphilis?

## Chapter 17 Questions - STDs.doc

- primary: 1<sup>st</sup> symptomatic episode
- secondary: refers to recurrences
- latent: periods after infection where pts are seroreactive but have no other signs or sx of the disease
- tertiary: formation of gummas and cardiovascular syphilis
- neurosyphilis: auditory or ophthalmic sx, meningitis, CN palsies, eye disease

### How can syphilis be diagnosed?

- **scrapings from base of chancre examined by darkfield or fluorescent Ab**
- FTA-ABS: fluorescent treponemal antibody absorption test
- MHATP: microhemagglutination assay for Ab to *T. pallidum*
- VDRL: Venereal Disease Research Laboratory → non-treponemal test
- RPR: rapid plasma reagin

### What is the treatment for syphilis?

- Primary / Secondary / Early latent syphilis  
→ benzathine penicillin G 2.4M units IM x 1 (50000U/kg in children)
- Late latent syphilis / tertiary syphilis  
→ 2.4M units IM qwk x 3
- Neurosyphilis  
→ aqueous crystalline pen G 3-4million U IV q4h x 10-14d
- re-examine for syphilis at 3-6months
- counselling for HIV

### What is the Jarisch-Herxheimer reaction?

- acute febrile reaction to erythromycin or ceftriaxone that may occur in the 1<sup>st</sup> 24 hrs after therapy  
→ accompanied by headache, myalgia, and other sx

### What is the etiology of lymphogranuloma venereum?

- caused by *C. trachomatis* serotypes L1, L2, L3

### Describe the physical findings in lymphogranuloma venereum.

- firm, painless lesion w/ low elevated borders
- painful inguinal LN a few weeks later  
→ associated w/ F/C, N/V, arthralgia  
→ skin rashes

### How can one diagnose lymphogranuloma venereum?

- culture of *C. trachomatis*  
→ best obtained from aspiration of fluctuant inguinal node
- bloodwork  
→ leukocytosis, anemia, elevated gamma globulins

### What is the treatment of lymphogranuloma venereum?

- doxycycline 100mg PO BID x 21d
- treatment for rectal strictures if present

### What is the etiologic agent in chancroid?

- *H. ducreyi*

### Describe the physical findings in chancroid.

- **painful lymphadenopathy** in 50%
- **painful ulcer** w/ deep undermined border  
→ soft, indurated, and purulent  
→ base of lesion friable and bleeds easily

### How can one diagnose chancroid?

- Gram stain smear: take from base of lesion  
→ gram-negative coccobacilli in chains w/ "school of fish" appearance
- culture of *H. ducreyi*

## **Chapter 17 Questions - STDs.doc**

### **What is the treatment of chancroid?**

- difficult due to antibiotic resistance – any of:
  - azithromycin 1g PO x 1
  - ceftriaxone 250mg IM x 1
  - cipro 500mg PO BID x 3d
- treat sexual partners

### **What is the etiologic agent in granuloma inguinale?**

- *Calymmatobacterium granulomatis*
  - grame –ve bacillus related to *Klebsiella pneumoniae*

### **Describe the physical findings in granuloma inguinale.**

- incubation period 1-12 weeks
- small papule seen first
  - forms as small ulcer above level of the skin
  - base of ulcer erythematous, may bleed
  - nontender, indurated, and firm

### **How can one diagnose granuloma inguinale?**

- identification of Donovan bodies on a stained smear
- crush specimen for histologic study
- biopsy
- **no culture available**

### **What is the treatment for granuloma inguinale?**

- Septra DS 1 tab PO BID x 3 weeks
- doxycycline 100mg PO BID x 3 weeks
- cipro 750mg PO BID x 3 weeks
- erythromycin 500mg PO QID x 3 weeks

### **What is the etiologic agent in genital warts?**

- DNA-containing virus of human papilloma species (HPV)
  - types 6 and 11 most often cause visible external warts

### **What is the prevalence of HPV infection?**

- 46% of college women

### **What is the goal of treatment in HPV infection?**

- remove exophytic warts
- decrease signs or sx pt may have from wart infection
- no therapy available to eradicate HPV
- biopsy all atypical pigmented or persistent warts

### **Describe the site-specific treatment for genital warts.**

- External genital, perianal, vaginal
  - primary: cryotherapy w/ liquid nitrogen
  - secondary: podophyllin 10-25% x 4 weeks, trichloroacetic acid 80-90% weekly
- Cervical: r/o dysplasia
- Meatal
  - primary: cryotherapy
  - secondary: podophyllin
- Urethral: cryotherapy, 5% 5-FU or thiotepa
  - do not use podophyllin
- Anorectal
  - primary: cryotherapy
  - secondary: surgical removal, trichloroacetic acid
- Oral: surgical removal

### **What is the etiologic agent in scabies?**

- mite: *Sarcoptes scabiei*

## Chapter 17 Questions - STDs.doc

### What are the sx of scabies?

- severe urticaria
  - worse at night, in bed
  - severe excoriation

### What is the treatment for scabies?

- permethrin cream (5%) to entire body – wash off after 8 hrs
- lindane 1% to entire body x 8-14hrs – cannot use if pregnant or lactating
- treat sexual partners
- wash clothing and bed linen on hot cycle to kill mites

### What is the etiologic agent for pediculosis pubis (phthiriasis)?

- crab louse

### How can one diagnose crabs?

- Hx: itching of haired portion of pubis, thighs, or scrotum
- Px: nits seen attached to hair shaft near skin surface – can be seen in axilla, eyelashes, or scalp

### What is the treatment for crabs?

- permethrin cream to affected areas x 10min
- lindane shampoo x 4min
- Septra
- treat sexual partners
- wash bed linens and clothing

### What is the etiologic agent for molluscum contagiosum?

- DNA pox virus
- associated w/ HIV infection

### What is the incubation period for molluscum?

- 2-3months

### How can one make a diagnosis of molluscum?

- small firm umbilicated papules on skin
  - smooth, pearly, or flesh coloured
- biopsy: molluscum bodies seen

### What are molluscum bodies?

- eosinophilic hyalin spherical masses seen on biopsy of molluscum

### What is the treatment for molluscum?

- curettage
- liquid nitrogen
- chemical eradication: cantharadin, phenol, iodine, silver nitrate, trichloroacetic acid
- treat sexual contacts

### What sexually transmitted agents can cause infections of the liver, intestines, or anorectum?

- Liver: hep A, hep B, hep C
- intestines: *Giardia*, *Entamoeba histolytica*, *Cryptosporidium*, *Shigella*, *Campylobacter*, *Strongyloides*
- Anorectum: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, HSV, HPV
- fecal contact from anal sex or anilingus

### What are the usual etiologic agents in acute proctitis after unprotected receptive anal intercourse?

- gonorrhoeae, chlamydia, HSV

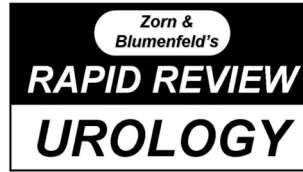
### What is a macrolide?

- a class of antibiotics that includes azithromycin, clarithromycin, erythromycin
- act by inhibiting protein synthesis, specifically by blocking the 50S ribosomal subunit

## **Chapter 17 Questions - STDs.doc**

### **How do tetracyclines/doxy and aminoglycosides work?**

- act by inhibiting protein synthesis by blocking the 30S ribosomal subunit



## **Chapter 18**

### **• AIDS and Related Conditions •**

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#### **Why is retroviral infection usually permanent?**

- infection w/ retrovirus seldom results in lysis of host cells

#### **Describe the physical characteristics of the HIV virus.**

- spherical shape, outer envelope, variable surface projections, icosahedral capsid containing ribonucleoprotein complexed w/ a core shell
- 72 projections protrude from virion surface – composed of glycoproteins: gp120 and gp41

#### **What are the replicative genes in the HIV genome?**

- gag: encodes structural proteins of capsid
- pro: encodes viral protease for cleaving precursor proteins
- pol: encodes reverse transcriptase and integrase enzymes
- env: encodes envelope glycoprotein

#### **What cells are the initial targets for HIV-1 infection?**

- macrophage or dendritic cells, or both

#### **How does HIV-1 gain entrance into the macrophage?**

- binds to surface of cell via gp120 molecule and CD4 protein on T<sub>H</sub> cells
- fusion of HIV-1 w/ cell membrane w/ 2<sup>nd</sup> receptor or coreceptor
- virus is then internalized, and viral RNA is released into host cytoplasm

#### **How is the HIV-1 RNA integrated into the host genome?**

- viral RNA in cytoplasm is transcribed by reverse transcriptase into linear dsDNA
- viral DNA transported into nucleus, and is integrated into the host genetic material via viral integrase protein

#### **How is HIV-1 virus produced from infected cells?**

- integrated viral DNA (provirus) is transcribed into mRNA by host cell RNA polymerase  
→ viral protease needed for proteolytic processing of protein precursors
- structural components of the virus are assembled at the cell surface
- mature virions bud from the cell surface and attach to other cells

#### **Why is HIV-1 so genetically diverse?**

- HIV-1 DNA polymerase is error-prone  
→ viral replication establishes a pool of genetic variants

#### **Why do the serum antibodies and cytotoxic T cells created by infected individuals do not lead to protection of the host?**

- hypervariable regions in the virus envelope mutate quickly
- leads to selection of variants of the virus that evade the host immune response

#### **Describe the role of lymphoid organ involvement in HIV-1 infection.**

- HIV-1 enters body and localizes in regional LN  
→ viremia during primary infection results in extensive dissemination to other lymphoid organs
- HIV-1 immune response leads to follicular hyperplasia and sequestration of infected CD4<sup>+</sup> cells in lymphoid organs  
→ lower levels of viral replication in blood  
→ active viral replication continues in lymphoid organs → clinical latency

#### **Describe the natural history of HIV infection.**

*Rapid Review Urology - Study Notes (Kevin C. Zorn & Aaron Blumenfeld, 6/2006©)*



## Chapter 18 Questions - AIDS.doc

- wide dissemination of virus during primary infection, seeding of lymphoid organs  
→ sharp decline in CD4+ count
- immune response accompanied by lower levels of culturable HIV in blood and long clinical latency (median 10 yrs)
- after critical reduction of systemic immune function, constitutional sx appear  
→ opportunistic diseases and malignancies seen  
→ death

### What are the problems in creating a vaccine for HIV-1?

- high degree of variability in HIV-1 strains  
→ most variable region in viral envelope
- no good animal model
- persons w/ natural infections develop Ab against HIV-1

### How can one classify antiretroviral chemotherapy?

- nucleoside analogue reverse transcriptase inhibitors  
→ zidovudine (thymidine analogue), didanosine (adenosine), zalcitabine (cytidine), stavudine (thymidine), lamivudine, abacavir
- non-nucleoside reverse transcriptase inhibitors  
→ nevirapine, delavirdine, efavirenz
- protease inhibitors  
→ saquinavir, indinavir, ritonavir, nelfinavir, amprenavir

### What are the advantages in treating HIV w/ protease inhibitors?

- ability to inhibit HIV replication in cells that are chronically infected
- synergism
- toxicity profiles

### What opportunistic infections allow for a definition of AIDS?

- bacterial infections (multiple/recurrent) in children < 13yrs
- candidiasis: esophageal/respiratory
- invasive cervical ca
- coccidiomycosis: disseminated or extrapulmonary
- cryptococcosis: extrapulmonary
- cryptosporidiosis: chronic intestinal
- CMV  
→ CMV retinitis  
→ disease other than liver, spleen, or nodes
- HIV encephalopathy
- HSV  
→ chronic ulcers  
→ bronchitis, pneumonitis, or esophagitis
- histoplasmosis: disseminated or extrapulmonary
- isosporiasis: chronic intestinal
- Kaposi's
- lymphoid interstitial pneumonia +/- pulmonary lymphoid hyperplasia in children < 13yrs
- lymphoma  
→ Burkitt's lymphoma  
→ immunoblastic lymphoma  
→ primary brain lymphoma
- MAI complex
- TB: any site
- PCP
- recurrent pneumonia
- progressive multifocal leukoencephalopathy
- Salmonella sepsis
- toxoplasmosis of brain
- HIV wasting syndrome

### How can one diagnose HIV-1 infection?

- detect Ab against HIV-1 antigens: ELISA

## **Chapter 18 Questions - AIDS.doc**

- polypeptide Ag of HIV-1 core and envelope

### **Describe the sx of HIV-1 infection.**

- initial infection
  - acute mononucleosis-like illness: fever, l/a, night sweats, myalgia, arthralgia, rash, malaise, lethargy, sore throat

### **How long does it take to develop AIDS after HIV infection?**

- w/o therapy, <5% of HIV-1 infected adults develop AIDS after 2yrs
- 20-25% w/i 6 yrs
- 50% w/i 10yrs

### **What is meant by the viral setpoint?**

- quasi-steady state of HIV-1 viral replication and clearance

### **What is the median survival in treated AIDS pts?**

- 2-3 yrs

### **How can one classify HIV-1 infection?**

- CDC system: based on CD4+ count and clinical sx
  - asymptomatic, acute HIV, or persistent generalized l/a (2 or more extrainguinal sites for >3months)
    - A1: CD4 > 500
    - A2: CD4 200-499
    - A3: CD4 <200
  - symptomatic, but not AIDS
    - B1: CD4 > 500
    - B2: CD4 200-499
    - B3: CD4 <200
  - AIDS-indicator conditions
    - C1: CD4 > 500
    - C2: CD4 200-499
    - C3: CD4 <200

### **What are the various modes of transmission for HIV-1?**

- direct sexual contact
- exposure to contaminated blood and blood products
- perinatal transmission

### **What is the risk of HIV-1 infection from a single heterosexual contact?**

- <0.1%

### **What are the RF for sexual transmission of HIV-1?**

- large # of sexual partners
- receptive unprotected anal intercourse
- genital ulcer disease
  - chancroid, syphilis, HSV
- uncircumcised
  - increased chance for balanitis

### **What populations are at risk for blood-borne transmission?**

- illegal IV drug use
- blood and organ recipient
- hemophiliac pt
- health care workers
- commercial sex workers
- prison population

### **What are the potential GU complications of HIV-1 infection?**

- infections
  - GU TB: kidney, bladder, ureter

## Chapter 18 Questions - AIDS.doc

- renal infections
  - CMV, Aspergillus, Toxoplasma gondii
- penile and urethral infections
  - genital HSV
  - Reiter's syndrome
  - PID
- prostatic infections
  - bacterial prostatitis and abscesses
  - CMV prostatitis
- testicular and epididymal infections
  - CMV, Candida
  - toxoplasmosis of testis
- malignancy
  - SCC
  - malignant melanoma
  - testis cancer
    - germ cell, lymphoma
  - Kaposi's sarcoma
  - NHL
  - invasive cervical cancer
- renal disease
  - HIV nephropathy
- urolithiasis
  - indinavir stones
- voiding dysfunction
  - retention, hyperreflexia, BOO
- Fournier's gangrene

### What is the most common testicular abnormality in AIDS?

- **testicular atrophy**
  - due to endocrine abnormalities, febrile episodes, malnutrition, toxic effects of therapeutic agents, or testicular infections

### What is the etiologic agent in Kaposi's sarcoma?

- HHSV-8

### What are the variants of Kaposi's sarcoma?

- spindle cell
- anaplastic
- mixed: most common in AIDS pts

### What is the natural hx of Kaposi's sarcoma in AIDS?

- **highly variable**
- progresses rapidly, often w/ visceral involvement

### What is the treatment for Kaposi's sarcoma?

- unclear
  - responds to radiation: less durable in HIV+ pts
- surgery
  - for primary lesion for diagnosis, or for lesions that bleed
- cytotoxic agents
  - liposomal anthracyclines, paclitaxel, vinca alkaloids, bleomycin, IFN

### What are the characteristics of HIV nephropathy?

- proteinuria
- elevated Cr
- FSGS on biopsy

### What is the treatment for indinavir urolithiasis?

- hydration

## **Chapter 18 Questions - AIDS.doc**

- analgesia
- stop indinavir

### **What are the indications for intervention in indinavir urolithiasis?**

- persistent fever
- intractable pain
- inability to tolerate PO liquids
- solitary kidney

### **What abnormalities on U/A are often seen in HIV+ pts?**

- hematuria
- pyuria
- bacteriuria
- proteinuria

### **What is the risk of seroconversion after a needlestick injury?**

- 0.3%

### **What is the risk of seroconversion after cutaneous exposure to HIV+ blood?**

- 0.09%

### **What factors increase the risk of seroconversion in health care workers?**

- exposure to blood from terminal AIDS pts
- visible, gross blood contamination
- contaminated needle placed directly into a vein
- deep injury
- hollow-bore needle

### **What factors determine the need for postexposure prophylaxis?**

- nature of exposure
- volume of blood or fluid
- viral load in pt
- potential for resistant strains in pt

### **What agent has been shown to prevent HIV transmission in humans?**

- zidovudine

### **What are the indications for HIV testing?**

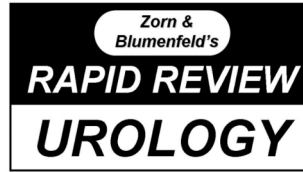
- evaluation of blood and organs for donation
- persons at risk for HIV
  - pts w/ STD, hx of illegal IV drug use, others who consider themselves at risk
  - pts w/ hx of sexual contact w/ homosexual men, multiple unsafe heterosexual contacts, hx of needle sharing
  - pts w/ sexual contact w/ pt w/ HIV
- pts w/ unscreened blood transfusion since 1977
- hx of STD including hep B
- hx of sx associated w/ HIV infection
- pts w/ active TB
- selected women of reproductive age: living in community w/ high HIV prevalence
- children of HIV+ mothers

### **What are the advantages and disadvantages of wider HIV testing?**

- advantages
  - can test for TB before loss of delayed hypersensitivity
  - early institution of antiviral chemotherapy can delay onset of symptomatic disease
  - can receive counseling in risk-reduction behaviour
  - can identify pts for research studies
  - early prophylaxis for health care workers after exposure
- disadvantages
  - may drive pts at highest risk away from the health care system
  - false-positive tests: disrupts pts lives

**Chapter 18 Questions - AIDS.doc**

- anguish and damage to relationships from uncertain test results
- widespread discrimination



## Chapter 19

### • **Cutaneous Diseases of the Male External Genitalia** •

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**What is the difference b/w a macule and a patch?**

- macule: flat lesion < 0.5cm
- patch: flat lesion > 0.5cm

**What is the difference b/w a papule, nodule, and plaque?**

- papule: elevated lesion < 0.5cm
- nodule: deeper-based papular lesion
- plaque: elevated lesion > 0.5cm

**What is the difference b/w a vesicle, a pustule and a bulla?**

- vesicle: fluid-filled palpable lesion < 0.5cm
- pustule: pus-filled palpable lesion
- bulla: fluid-filled lesion > 0.5cm

**What is the difference b/w an erosion and an ulcer?**

- erosion: lesions representing only the loss of epidermis
- ulcer: lesion representing loss of epidermis and at least superficial dermis

**What is the differential dx of a papulosquamous lesion?**

- psoriasis
- seborrheic dermatitis
- dermatophyte infection
- erythrasma
- secondary syphilis
- pityriasis rosea
- discoid lupus
- mycosis fungoides
- lichen planus
- fixed drug reaction
- Reiter's syndrome
- pityriasis versicolor
- Bowen's disease
- extramammary Paget's disease

**Describe the characteristic lesions of psoriasis.**

- red to pink plaques or patches covered w/ white to gray scale  
→ scale may not be present in skin folds and on moist/mucosal surfaces
- lesions most commonly on elbows, knees, scalp, umbilicus, nails, and buttocks  
→ **genital structures affected most commonly: hair-bearing structures and perirectum**
- lesions may be pruritic or tender

**What is the natural hx of psoriasis?**

- chronic lifelong disease w/ periods of exacerbation and remission  
→ improvement w/ topical emollients or steroids

**What is the tx of psoriasis?**

- topical emollients
- low-potency topical steroids → no longer than 2 weeks if on genital skin

## Chapter 19 Questions - GU Derm.doc

- may result in cutaneous atrophy, striae formation, proliferation of cutaneous fungi, and skin dependency reaction
- other topical tx: anthralin, calcipotriene, retinoids, tar
- systemic tx: methotrexate, etretinate, psoralen, UVB, CSA

### Describe the characteristic lesions of lichen planus.

- pruritic inflammatory disease of the skin
  - flat-topped violaceous polygonal papule
  - multiple lesions from 2-5mm in diameter
  - lesions may ulcerate, esp on macerated and mucosal surfaces
- occurs on trunk, flexor aspects of limbs, oral mucosa, and glans penis
  - glans lesions tend to be solitary and few: may be ringlike

### What is the cause of the lesion in lichen planus?

- due to the result of T cell interaction in the skin
  - lichenoid reactions can occur in response to ingestants
  - dx based on clinical observation, unless ulcer present
    - pathologic confirmation required

### What is the tx of lichen planus?

- usually resolves spontaneously
- asymptomatic lesions do not require tx
- topical steroids
- systemic immunosuppressants: PO steroids

### Describe the characteristic lesions of lichen nitidus.

- uncommon chronic inflammatory disease of unknown etiology
  - may be a variant of lichen planus
- very small flat-topped flesh-coloured to pink or yellow-red papules
- lesions usually on penis, lower abdomen, and arms
- lesions may appear follicular: are not
- occur in sites of local trauma
- rarely coalesce into larger lesions

### What is the tx of lichen nitidus?

- usually spontaneously resolves
- steroids, psoralen-UVA, etretinate

### What is Reiter's syndrome?

- seronegative spondyloarthropathy: systemic illness that involves several soft and hard tissues, associated w/ HLA-B27
- more common in men
- associated w/ preceding urethritis (*Gonococcus* or *Chlamydia*) or enteritis (*Shigella*, *Salmonella*, *Campylobacter*, *Neisseria*, or *Ureaplasma*)
- more common in pts w/ HIV
- triad of arthritis, cervicitis / urethritis / enteritis and conjunctivitis / iritis of 1 months duration

### Describe the characteristic lesions of Reiter's syndrome.

- similar to plaquelike and pustular psoriasis
  - lesions commonly occur on glans penis, are circinate, and are eroded (*circinate balanitis*)
- similar lesions on other mucosal membranes
- hyperkeratotic lesions of hands/feet (**keratoderma blennorrhagicum**)

### What is the management of Reiter's syndrome?

- look for *Chlamydia* in every case of Reiter's
- arthrocentesis to r/o infectious monoarthritis
- NSAIDs, sulfasalazine for arthritis
- genital lesions usually self-limited, may respond to topical steroids
- antibiotics for urethritis: GC or NGU
- systemic agents: MTX, CSA, steroids

### What are the most likely drugs to cause a fixed drug eruption?

## Chapter 19 Questions - GU Derm.doc

- BCP, barbiturates, phenolphthalein, tetracycline, salicylates, NSAIDs

### Describe the characteristic lesions of a fixed drug eruption.

- solitary, well-demarcated inflammatory plaques that occurs in reaction to PO medication  
→ may become erosive
- lesions frequently on shaft and glans penis → painful, may be misdiagnosed as herpes
- post-inflammatory hyperpigmentation

### Describe the characteristic lesions of seborrheic dermatitis.

- lifelong affliction w/ periods of exacerbation and remission
- lesions on hair-bearing surfaces, have a red base, and often have a waxy yellow crust: dandruff
- usually found on scalp, eyebrows, nasolabial folds, ears, chest  
→ also on penis, anus, pubic hair areas

### What is the etiology of seborrheic dermatitis?

- unknown: *Pityrosporon orbiculare* implicated as causative agent

### What is the tx of seborrheic dermatitis?

- frequent shampooing of involved hair-bearing areas
- antidandruff shampoos: Zn, salicylic acid, Se, tar, ketoconazole
- topical antifungals
- topical low-potency steroids

### Describe the characteristic lesion of lichen sclerosis.

- chronic dermatitis: a.k.a. lichen sclerosis et atrophicus  
→ late stage: BXO
- well circumscribed porcelain-white macules or plaques
- hyperkeratotic scales can occur
- epidermis often atrophic, crinkles, and is prone to shear injury → ulceration
- lesions most common on moist skin of foreskin, vulva, or perianal region  
→ dermis eventually becomes sclerotic → atrophic scar
- destruction and contraction of foreskin, clitoral prepuce, and vulva may occur
- can occur on other parts of body: trunk, upper arms, chest, abdomen
- usually limited to men > 60yrs

### How can one diagnose lichen sclerosis?

- clinical findings  
→ histologic confirmation: basal cell layer vacuolization, epidermal atrophy, dermal edema, homogenization of collagen in papillary dermis, focal perivascular infiltrate in the dermis, and plugging of ostia of follicular and eccrine structures

### What is the tx of lichen sclerosis?

- circumcision
- topical tx: usually no more effective than placebo  
→ estrogen, progesterone, testosterone, antimicrobials, vaseline, and antifungal agents  
→ high potency topical steroids: effective in women

### Describe the characteristic lesion of eczematous or allergic dermatitis.

- eruptions confined to outer layer of skin
- skin red, weepy, may have crusts
- itch: pt scratches w/o realizing it  
→ worsens during stress, evenings, in relation to seasons or allergens  
→ frequently associated w/ seasonal allergies, asthma, FHx atopy
- skin thickens (lichenifies) and develops pigmentary changes
- common sites on men: scrotum

### What is the differential dx of eczematous dermatitis?

- eczema
- allergic dermatitis



## Chapter 19 Questions - GU Derm.doc

- seborrheic dermatitis
- intertrigo
- contact dermatitis
- irritant dermatitis
- balanoposthitis
- Zoon's balanitis
- Candidal-related illness
- impetigo
- HSV
- HZV
- drug reaction

### What is the tx of atopic eczema?

- quenches pts desire to scratch
- avoid tight, irritating clothing
- infrequent bathing w/ tepid water, mild soap, minimal scrubbing
- bland moisturizer
- topical steroids
- systemic agents: antihistamines, TCAs

### What is contact dermatitis?

- skin's response to an externally applied agent
  - due to irritant dermatitis or allergen dermatitis

### Describe the characteristic lesions of contact dermatitis.

- cutaneous reaction → localized inflammation → scale and crust formation
  - severe reaction: blistering and tissue necrosis
  - itchy, burning, sting
- irritant dermatitis
  - occurs almost immediately after exposure to offending agent: directly damages cutaneous tissues
  - common in industry w/ solvents, acids, alkali
  - severe full-thickness wounds
- allergic dermatitis
  - immune-mediated response to topical application of contactant
  - type IV delayed hypersensitivity response → may be days after exposure
  - ex: poison ivy, nickel

### What is the tx of contact dermatitis?

- removing offending agent
- low-potency topical steroids
- PO antihistamines or steroids
- debridement and grafting if severe

### Describe the characteristic lesions of erythema multiforme.

- major variant (Stevens-Johnson syndrome)
  - targetoid lesions, blisters, and mucosal membrane involvement
  - toxic epidermal necrolysis (TEN): skin sloughing, blisters
- minor variant
  - red 1-2cm targetoid lesions
  - all cutaneous surfaces may be involved

### What is the etiology of EM?

- generalized skin disease, most frequently caused by ingestants: antibiotics (Septra), antiseizure meds
- can be due to infections (ex: HSV) and hormonal fluctuations

### What is the tx of EM?

- eliminate causative agent
- treat denuded skin → burn unit if needed
- systemic immunosuppression controversial

## Chapter 19 Questions - GU Derm.doc

### What is the differential diagnosis of erosive lesions?

- bullous pemphigoid
- pemphigus vulgaris
- pemphigus foliaceus
- Zoon's balanitis
- Behcet's syndrome
- contact dermatitis
- dermatitis herpetiformis
- porphyria cutanea tarda
- HZV
- HSV
- lymphangioma circumscriptum
- impetigo
- fixed drug eruption
- factitial
- innocent trauma
- benign familial pemphigus

### What is pemphigus vulgaris?

- immune-mediated blistering eruption
- due to IgG autoAb **produced against cell surface of keratinocytes**
- usually after 5<sup>th</sup> decade
- flaccid blisters on multiple body parts, including mucosal membrane
- tx w/ immunosuppressives

### What is Hailey-Hailey disease?

- benign familial pemphigus
- AD vesicular eruption
- occurs in intertriginous areas
- vesicles formed by loss of keratinocyte cell adhesion → superinfected and denude → crust
- tx: local excision, grafting, topical antibiotics and drying agents, systemic steroids

### What is bullous pemphigoid?

- immune-mediated blistering eruption, most common in pts > 60
- due to IgG autoAb **produced against 230kD protein in lamina** (bullous pemphigoid antigen)
- large tense blisters on several different cutaneous sites  
→ may involve mucosal membranes
- treat w/ systemic immunosuppression: PO steroids, CSA, azathioprine, MMF

### What is dermatitis herpetiformis?

- immune-mediated blistering eruption
- due to IgA autoAb **against basement membrane**
- intensely painful lesion: burning, pruritic papule or vesicle
- lesions on elbows, knees, buttock, shoulders, sacrum
- associated w/ gluten-sensitive enteropathy
- tx: dapsone, gluten-free diet

### What is the differential dx of ulcers?

- syphilis
- chancroid
- HSV
- Crohn's
- aphthous ulcer
- Behcet's disease
- granuloma inguinale
- lymphogranuloma venereum
- factitial dermatitis
- Wegener's granulomatosis

## Chapter 19 Questions - GU Derm.doc

- leukocytoclastic vasculitis
- pyoderma gangrenosum

### How does IBD/Crohn's most often involve the rectum and genitalia?

- extends as fistula from bowel to perirectal area

### What is pyoderma gangrenosum and describe its characteristic lesion?

- chronic painful ulcerating disease associated w/ Crohn's, UC, or collagen vascular disease
- lesions occur on lower extremity, or anywhere
- lesions can occur at site of trauma
- wounds are exudative and have a violaceous border
- lesions may begin as purple nodules or blisters

### What is the tx of pyoderma gangrenosum?

- good wound care
- immunosuppression: steroids, CSA

### What is Behçet's disease?

- syndrome characterized by oral and genital ulcers, uveitis, and non-mucous membrane skin lesions
- unknown cause
- associated w/ aneurysms, arthritis, thrombophlebitis, GI, neuro, and psych problems
  - major criteria: oral ulcers
  - 4 secondary criteria: (SOUP)
    - Skin lesions
    - Ocular involvement
    - Ulceration: recurrent genital ulceration that heals w/ scarring
      - ◆ painful
      - ◆ herpetiform, major (>1 cm), or minor (<1 cm)
      - ◆ aphthous-like: superficial and circular/oval
    - Pathergy (sterile erythematous papule > 2mm appearing 48 hours after skin pricks with sharp needle)

### What is the tx of Behçet's disease?

- local: moisture-retaining dressings, intralesional injections of steroids, topical anaesthetics
- systemic: steroids, azathioprine, CSA, colchicine, MTX, cyclophosphamide, FK-506, plaquenil, thalidomide

### What are aphthous ulcers?

- small painful erosions usually in oral mucosa
- may be found on penis and scrotum: may be related to Behçet's disease
- no good tx: resolves spontaneously

### Describe the characteristic lesions of CIS.

- aka erythroplasia of Queyrat: if involves glans, prepuce
  - Bowen's disease: if involves remainder of genitals or perineal region
- keratinizing skin: scaly
- mucosal skin: no scale
- pruritic, painful, solitary, slowly enlarging

### What is the DDx of penile CIS?

- don't FAINT if you see this on your Penis, Bob.
  - Fixed drug eruption or other drug-induced dermatoses
  - Allergic/irritant contact dermatitis
  - Infection
  - Neoplasia
  - Trauma
  - Psoriatic/systemic disorders
  - Balanitis (specific types)

### What is the tx of penile CIS?

- tissue destruction

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- cryotherapy, topical vesicants, laser, excision
- fluorouracil (Efudex) cream: blocks the methylation of deoxyuridylic acid and inhibits thymidylate synthetase, which subsequently reduces cell proliferation

### What is bowenoid papulosis?

- benign lesion histologically similar to penile CIS
- causal association b/w this and HPV 16
  - increased risk in female partners of men w/ bowenoid papulosis
- multiple erythematous papules < 1cm → may coalesce to form plaques

### Describe the characteristic lesions of Kaposi's sarcoma.

- violaceous to light brown lesions
  - macules, papules or plaques
  - may ulcerate
  - may get significant local edema

### What is the tx of penile Kaposi's?

- intralesional injection of chemo
- rads
- topical aliretinoin gel
- local tissue destruction

### What is pseudoepitheliomatous keratotic and micaceous balanitis?

- solitary slowly enlarging white thick hyperkeratotic plaque
- typically on glans penis
- must differentiate from SCC
- treat w/ removal

### Describe the characteristic lesions of BCC.

- papular, pearly w/ telangectasias
- may ulcerate

### Describe the characteristic lesions of extramammary Paget's disease (EMPD).

- primary cutaneous adenocarcinoma, usually on vulva or anus: infrequently on penis
- pruritic erythematous plaque, may become large and extend on > 1 genital surface
- lesions may excoriate and encrust
- must differentiate from benign papulosquamous disorders

### What is the tx of extramammary Paget's?

- biopsy of lesion: see vacuolated Paget cells
- complete evaluation for underlying carcinoma
- surgical removal of plaque
- rads
- topical tx w/ 5-FU

### What is cutaneous T cell lymphoma?

- uncommon lymphoproliferative malignancy of T cell origin
- lesions start as nonspecific pruritis
  - may mimic eczema, psoriasis, lichen simplex chronicus, contact dermatitis
- may go on to fungating plaquelike lesions, erythroderma, ulcers, erosions and hematologic involvement (**Sezary's syndrome**)
- associated w/ HIV infection
- may involve genital skin
- tx: steroids, topical nitrogen mustard, phototherapy, IFN, photopheresis, PO retinoids

### What is erythrasma?

- infection from *Corynebacterium minutissimum*
- sharply bordered, red/brown, scaling eruption of intertriginous areas
  - usually on crural areas b/w scrotum and thigh and axillae

## Chapter 19 Questions - GU Derm.doc

- groin lesions asymptomatic
- produces porphyrin that produces red fluorescence under Wood's lamp
- tx: PO erythromycin, topical antifungal creams

### What is trichomycosis?

- bacterial infection of the hair in intertriginous areas
- pts usually suffer from hyperhidrosis
- discrete nodules on hair
- tx: alleviate hyperhidrosis, topical antibiotics

### What is balanoposthitis?

- inflammation of foreskin and glans
- redness, edema, discharge, pain
- tx: eliminate offending agents, skin care, topical antibiotics, topical antifungals, low-potency topical steroids

### What is hidradenitis suppurativa?

- chronic suppurative disease of the apocrine gland-bearing areas of the body
- in groin, axillae, and buttocks
- lesions: red nodules, papules, or cysts
- tends to occur in pts w/ acne vulgaris
- occurs due to keratin plugging of follicles w/ associated inflammation of apocrine gland
- tx: tetracyclines, erythromycin, steroid injections

### What is folliculitis?

- small red papules or pustules over hair-bearing structures
- due to follicular irritant from external trauma or topical irritants or from Staph infections

### What is a furuncle?

- red, fluctuant, tender, painful, perifollicular pustule or abscess
- usually due to local cutaneous infection w/ *Staph aureus*
- tx: I&D if large

### What is the difference b/w erysipelas and cellulitis?

- erysipelas: superficial infection of skin generally not involving layers deeper than dermis
  - skin at border of lesion is raised and sharply demarcated from normal skin
  - more common in newborns and elderly ppl
- cellulitis: skin infection involving cutaneous layers as deep as subcutaneous layers
  - borders are indistinct and blurred
- both usually due to Gp A strep, occ. due to Staph

### What is ecthyma gangrenosum?

- necrotic cutaneous eruption related to pseudomonal sepsis
- vesicles on violaceous base → progresses to necrotic ulcer
- located on buttocks, inguinal crease, and lower extremity
- tx: antipseudomonal antibiotics

### Describe the characteristic lesions of candidal intertrigo.

- red perirectal and intertriginous skin
- fissures in red areas
- small papules and pustules
- satellite lesions
- pruritis
- dx: KOH scraping
- tx: removing cause of macerated skin → talc, cornstarch, cotton clothes, topical antifungals

### What is "jock itch?"

- tinea cruris: dermatophyte infection
- fungi live in superficial layers of epidermis
- usually due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*

## Chapter 19 Questions - GU Derm.doc

- dx: KOH scraping
- tx: antifungals

### What organisms usually cause infestation of humans?

- pediculosis pubis (*Phthirus pubis*) = crabs
- scabies
  - pruritic papular and linear burrow-like lesions
  - found in finger webs, axillae, umbilicus, anus, flexure area of arm/wrist/leg, genitals, areolae
  - scalp and face are spared
  - tx: lindane, permethrin, precipitated sulfa, crotamiton cream

### What is the angiokeratoma of Fordyce?

- seen on scrotum, glans, shaft
- small ectasias of blood vessels
- red/purple 1-2mm papules
- benign lesions
- tx: electrodesiccation or topical coagulants if bleeding

### Describe the characteristic lesion of penile melanosis.

- rare pigmented macule of the penis
- irregular border, large, light brown to tan to black and blue
- bx to r/o malignancy

### What is sclerosing lymphangitis?

- translucent cordlike lesion that occurs on shaft or glans
- seldom painful
- flesh coloured or slightly red
- associated w/ vigorous sexual activity
- tx: avoid vigorous sex, remits in few weeks

### What is Zoon's balanitis?

- **plasma cell** balanitis, manifests as lesion on glans or prepuce
- seen only in uncircumcised men
- patchlike lesion, solitary and red w/ distinct borders
- asymptomatic but chronic
- must differentiate from SCC

### What common benign cutaneous disorders are seen on the genitals?

- skin tag
- seborrheic keratosis
  - hyperplasia of epidermis
- dermatofibroma
- neurofibroma
  - evaluate for neurofibromatosis
- capillary hemangioma
  - tumour-like growths of blood vessels
- lymphangiectasia
- superficial lymphatic malformation
- acanthosis nigricans
- vitiligo
- postinflammatory pigment changes
- mole (nevus)

### What is acanthosis nigricans?

- velvety hyperpigmented poorly demarcated asymptomatic skin lesion
- in skin fold areas
- "dirty" appearance
- associated w/ heredity, endocrinopathies (insulin resistance), obesity, meds (niacin), GI/prostate/ovarian/lung ca
- no treatment

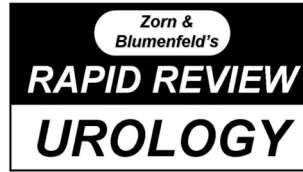
## **Chapter 19 Questions - GU Derm.doc**

### **What are the possible treatments for vitiligo?**

- may resolve spontaneously
- PO/topical steroids
- topical UVB
- skin graft
- bleaching
- cosmetics
- counselling

### **How can one classify nevi?**

- by location
  - junctional: b/w epidermis and dermis
  - dermal
  - compound: cluster of cells in both areas
- congenital vs. acquired
- dysplastic



## Chapter 21

### • TB and Parasitic Diseases of the GU System •

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**What was TB known as in the past?**

- "consumption"

**What is the most common opportunistic infection in AIDS?**

- TB

**What is the probability that an HIV-infected person with a hx of TB will develop active TB?**

- 10% per year

**How are most *M. tuberculosis* infections acquired?**

- inhalation of aerosolized droplet nuclei which reach the alveoli

**What are the determinants of infection probability for TB?**

- duration of exposure to source case
- size of bacterium inoculum inhaled
- infectivity of mycobacterial strain

**What is the probability of a competent host developing active TB after infection?**

- 5-10% over the persons lifetime
  - 50% occurs w/i 1<sup>st</sup> 2 years
  - all pts w/ AIDS get TB if infected

**Describe the pathogenesis of TB infection.**

- initial primary pulmonary infection
  - TB organisms multiply and evoke an inflammatory response
  - rapid spread occurs via lymphatics and blood stream
  - after 4 weeks, multiplication and dissemination decreases
- dormant bacilli
  - produce disease years later, after disease, trauma, steroid use, immunosuppressive therapy, DM, AIDS
- extrapulmonary TB
  - metastatic spread of organisms hematogenously during primary infection

**Describe the ultrastructure of the TB organism.**

- small bacilli w/ thick wall separated from cell membrane by a translucent zone
- no true capsule or flagellum → nonmotile
- cell wall is a complex structure made of 4 layers
  - innermost: peptidoglycan
  - 3 layers of peptides, polysaccharides, and lipids in homogenous matrix

**What living organisms can act as a reservoir for TB?**

- humans are the only reservoir

**What organisms make up the *M. tuberculosis* complex?**

- *M. tuberculosis*
- *M. bovis*
- *M. microti*
- *M. africanum*

**What is the behaviour of non-tuberculous mycobacteria?**

- rarely cause disease in GU system

**Rapid Review Urology –Study Notes (Kevin C. Zorn & Aaron Blumenfeld, 6/2006©)**



## Chapter 21 Questions - GU TB.doc

- often resistant to 1 or more of the 1<sup>st</sup> line drugs

### Describe the pathogenesis of renal TB.

- usually caused by activation of a prior blood-borne metastatic renal infection
- organisms in kidney settle in blood vessels, usually close to glomeruli
- macrophages appear
- caseating granulomas develop → consist of Langerhans giant cells surrounded by lymphocytes and fibroblasts  
→ if continue to multiply, cause central area of caseous necrosis
- **healing process causes fibrous tissue and calcium salts being deposited, producing the classic calcified lesion**
- lesions eventually slough into collecting system  
→ may increase in size until they reach a papilla, which is invaded and destroyed  
→ calyx ulcerates, causing the typical ulcerocavernous lesion
- fibrous tissue causes strictures in calyceal stem or at the UPJ  
→ chronic abscesses form in parenchyma

### Why is long-term monitoring of renal lesions required in renal TB?

- sudden increase in size may occur that requires surgical intervention → greater than 10 years

### What is the treatment of the renal lesions in renal TB?

- large areas of calcification should be excised
- nonfunctioning kidneys w/ extensive calcification should be removed

### What are the complications of renal TB?

- calyceal stricture
- UPJ obstruction
- fistulae
- hypertension  
→ unilateral TB and decreased renal blood flow  
→ treat w/ nephrectomy: 2/3 pts w/ extensive unilateral TB nephropathy have BP drop

### What is the site most commonly affected in tuberculous ureteritis?

- UVJ  
→ seen rarely in middle 1/3 of ureter  
→ treat w/ NUU

### Describe the pathogenesis of bladder TB.

- early infection start around UO → red, inflamed, edematous  
→ bulbous granulations appear and obscure UO
- TB ulcers may form: rare and late  
→ irregular and superficial  
→ central inflamed area surrounded by raised granulations  
→ initially close to UO, appear anywhere later on
- fibrosis starts around UO  
→ contracts to form stricture or becomes withdrawn rigid and dilated (classic golf-hole appearance)  
→ ureters rigid in lower 1/3 → always get VUR
- may get entire bladder covered w/ granulation and ulceration
- **may develop fistulae into rectum**

### Describe the management of TB of the testis.

- testicular swelling: impossible to differentiate from tumour  
→ exploration required if no response to antituberculous medication  
→ if orchitis secondary to TB epididymitis, testicular lesion responds rapidly to chemo after the epididymis removed

### Describe the presentation of TB epididymitis.

- usual presentation is inflamed painful scrotal swelling  
→ may be only presentation of GU TB  
→ usually starts in globus minor: greater blood supply than other parts of the epididymis
- may be generalized epididymal induration w/ beading of the palpable vas and testicular involvement
- may be a discharging sinus

## Chapter 21 Questions - GU TB.doc

- dx made after culture from discharging sinus or after epididymectomy

### What is the treatment of TB epididymitis?

- Septra x 2-3 weeks
  - if no improvement, start antituberculous medication
  - if lesion becomes nodular after 2-3 weeks, exploration of lesion is mandatory → seminoma has been reported

### Describe the presentation and treatment of penile TB.

- presents as superficial ulcer of the glans
  - indistinguishable from malignancy
- can progress to tubercular cavernositis w/ urethral involvement
  - dx confirmed by biopsy
- treat w/ antituberculous medications
- urethral TB: rare, treat urethral strictures as like any others, give antiTB meds

### What are the clinical features of GU TB?

- Hx
  - **vague, long-standing GU sx w/ no obvious cause → intermittent**
  - nighttime frequency, no dysuria
  - urgency if bladder involvement
  - SP pain rare
  - renal colic rare
  - hematospermia
  - recurrent cystitis
  - painful testicular swelling
  - incidentally found after TURP occasionally
- Labs
  - urine C&S -ve
  - WBC on R&M
  - microscopic hematuria: up to 50%
- Epidemiology
  - males > females
  - uncommon in kids

### How does one interpret a TB skin test?

- max inflammatory reaction occurs b/w 48 and 72 hrs after injection
- measure induration

### What are the criteria for TB positivity by risk group?

- Reaction > 5mm induration
  - HIV+ pts
  - recent contacts of TB pts
  - fibrotic changes on CXR consistent w/ previous TB
  - transplant and other immunosuppressed pts
- Reaction > 10mm induration
  - recent immigrants
  - IV drug users
  - residents/employees of: prisons, nursing homes, long-term care facilities, homeless shelters
  - TB laboratory personnel
  - pts w/ silicosis, DM, CRF, leukemia, lymphoma, ENT or lung ca, wt loss > 10% body wt, gastrectomy, jejunioileal bypass
  - kids < 4 yrs
  - kids < 18 exposed to high risk pts
- Reaction > 15mm induration
  - ppl w/ no risk factors

### What is the meaning of a +ve TB skin test?

- considered an indication that the person has been infected
- cannot be used as an indication for active TB

## Chapter 21 Questions - GU TB.doc

### How does one examine the urine for evidence of GU TB?

- R&M
  - RBC, WBC, pH, concentration
- C&S
  - secondary infection
- specific TB tests
  - **3-5 consecutive early morning urine specimens**
    - **Lowenstein-Jensen culture medium:** isolates *M. tuberculosis*
    - **pyruvic egg medium containing penicillin:** identify *M. bovis*
    - should be done quickly: longer the urine touches the organism, less likely it will grow
  - p-nitro- $\alpha$ -acetylamino- $\beta$ -hydroxypropriophenole test used to differentiate *M. tuberculosis* from other non-TB

### What are the radiologic tests that can be used for dx of GU TB?

- CXR
- KUB: important to look for calcification
- IVP
- retrograde
- perc + nephrostogram
  - important alternative to retrograde
  - useful in visualization of nonfunctioning kidney or determining condition of excretory pathway above an obstruction
- arteriography
  - limited value
  - used occasionally to assess amount of renal parenchymal damage to delineate renal arterial circulation
- renal scan
  - gives info on functional renal tissue, extent of disease
- MRI: little use
- endoscopy: not important in dx → used to assess extent of disease or response to chemo
  - biopsy only to dx TCC
- US: limited value
- CT: limited value

### What are the signs of TB on AXR?

- calcification in renal areas and in lower GU tract
- tuberculous ureteral calcification: cast of the ureter, which is thickened and not dilated
  - differentiate from schistosomiasis: mural calcification w/ dilated tortuous ureter

### What are the signs of TB on IVP?

- Kidney
  - small kidney
  - autonephrectomy
  - stones
  - caliectasis
  - moth-eaten distortion of calyx: earliest sign
  - fibrosed and occluded calyx (amputated calyx)
  - multiple small calyceal deformities
  - papillary necrosis
  - granulomata
  - cavitations: severe calyceal and parenchymal destruction
  - calcification in renal areas, and in lower GU tract
  - Kerr's kink: hiked up pelvis
- Ureter
  - tuberculous ureteritis: dilation above a UVJ stricture or rigid fibrotic ureter w/ multiple strictures
  - stricture: sawtooth type, beaded or corkscrew
  - filling defects
- Bladder
  - calcification
  - watering can perineum
  - small contracted bladder (**thimble bladder**)

## Chapter 21 Questions - GU TB.doc

### What are the indications for retrograde pyelogram in GU TB?

- rarely necessary
  - stricture at lower end of the ureter
    - delineate length of stricture
    - amount of obstruction and dilation above stricture
  - ureteral catheterization to obtain urine samples for culture from each kidney to localize

### How does one perform cystoscopy in a pt w/ GU TB?

- must be done under GA: prevent hemorrhage
- bladder filling must be done under direct vision

### What are the indications and contraindications for bladder biopsy in GU TB?

- Indications
  - pts w/ tubercles
  - ulcers far from UO → to diagnose TCC
- Contraindication
  - **acute bladder TB**

### What is the role of US in GU TB?

- limited value
  - used to monitor renal lesions seen on IVP
  - monitor volume of contracted bladder during tx

### What are the first-line antituberculous drugs?

- Bactericidal
  - rifabutin 150-300mg PO
  - INH (isoniazid, or isonicotinic acid hydrazide) 300mg PO/IM
  - rifampin 600mg PO/IV
  - rifapentine 600mg PO twice weekly
  - pyrazinamide 1.5-2.5g PO
  - streptomycin 15 mg/kg IM (about 1g)
- Bacteriostatic
  - ethambutol 15-25mg/kg PO (1-2g)

### What are the mechanisms of action of each of the antituberculous agents?

- INH: inhibits synthesis of mycolic acids by affecting the enzyme mycolase synthetase
- rifampin: antibiotic that inhibits bacterial RNA synthesis by inhibiting RNA polymerase
- pyrazinamide: inhibits fatty acid synthesis via fatty acid synthetase
- ethambutol: inhibits cell wall synthesis by blocking arabinosyl transferase
- streptomycin: aminoglycoside → inhibits protein synthesis by binding to 30S subunit of ribosome
- amikacin: inhibits protein synthesis
- capreomycin: inhibits cell wall synthesis
- quinolones: inhibits DNA gyrase

### What are the side effects of each of the antituberculous agents?

- INH
  - hepatic toxicity: 10-20% of pts → seen as increase in AST/ALT 6-8 weeks after tx
    - severe hepatic necrosis
  - peripheral neuropathy: due to enhanced pyridoxine excretion
    - prevented by daily supplemental PO pyridoxine (vitamin B<sub>6</sub>)
- rifampin
  - hepatotoxicity
  - flulike syndrome
  - significant drug interactions: BCP, steroids, antiretrovirals, other medications that are metabolized by cytochrome P-450
- pyrazinamide
  - arthralgias
  - hepatotoxicity

## Chapter 21 Questions - GU TB.doc

- hyperuricemia
- N/V
- ethambutol
  - retrobulbar neuritis
  - changes in visual acuity, red-green color perception: test q4-6weekly
- streptomycin
  - vestibular and ototoxicity
  - renal damage

### What is the most important principle in antituberculous therapy?

- multi-drug therapy to decrease the duration of therapy and decrease the chance of drug-resistant organisms

### In which forms of TB is a 6-month regimen not effective (MDR TB)?

- disseminated TB
- TB osteomyelitis
- TB meningitis

### What is the treatment for drug-sensitive TB?

- pts seen weekly on outpt basis, then q3mo after chemo finished
  - LFTs, 3-5 morning urines inspected (check to see if urine orange from proper rifampin usage)
- surgery scheduled electively if required
- pulmonary
  - rifampin 450mg, INH 300mg, pyrazinamide 25mg/kg x 2months
    - streptomycin adds nothing during initial phase
  - rifampin 900mg, INH 600mg x 4 more months
- GU
  - as above for 6-9 months total
    - streptomycin may be useful in pts w/ extensive disease and severe bladder sx
  - steroids may be helpful in acute tuberculous cystitis → prednisolone 20mg PO TID x 4 weeks
  - cycloserine: fastest acting, used in BCGosis
- No surgery:
  - minor radiologic lesion or moderate ulcerocavernous lesion → 6 mo chemo, F/U x 1 year, d/c if no recurrence
  - severe disease too extensive for OR: chemo w/ constant monitoring
- Surgery:
  - moderate ulcerocavernous lesion
  - severe lesion
    - w/ calcification: partial nephrectomy + 6 mo chemo, review annually for 10 years w/ Xray
    - w/o calcification: 6mo chemo, review q6mo for 5 years

### What are the RF for multidrug resistant TB?

- prior tx for TB
- residence in countries w/ high TB rates: India, Russia, Dominican
  - treat for 18-24mo, or 12 mo after cultures -ve

### What are the indications for nephrectomy in GU TB?

- nonfunctioning kidney (+/- calcification)
  - mandatory nephrectomy: never possible to salvage
- extensive disease involving the whole kidney + htn + UPJO
- coexisting RCC
- NUU: only if need to remove diseased ureter

### What are the indications for partial nephrectomy in GU TB?

- localized polar lesion w/ calcification that has failed to respond after 6 weeks of intensive chemo
- area of calcification that is slowly increasing in size and is threatening to gradually destroy the whole kidney
  - **never perform partial nephrectomy if there is no calcification** → treat w/ medication

### What is the role of abscess drainage in GU TB?

- no role for open drainage: perc drainage only

## **Chapter 21 Questions - GU TB.doc**

### **What are the indications for epididymectomy in GU TB?**

- caseating granuloma that does not respond to chemo
- firm swelling that has remained unchanged or has slowly increased in size despite antibiotics and antiTB meds

### **What is the management of ureteral stricture in GU TB?**

- Ix
  - retrograde ureterography to assess stricture length
- UPJ stricture
  - double-J stent initially
    - perc NT if not possible: pelvis irrigated w/ antiTB drugs
  - if significant deterioration, immediate surgery performed
    - pyeloplasty
    - reconstruction of sinus
    - endopyelotomy: not known
- stricture of middle 1/3
  - Davis intubated ureterotomy or double-J stent
  - recurrence common: IVP q3mo x 1 yr
- stricture of lower 1/3
  - if due to edema: respond to chemo
    - if no response after 3/52, add steroids to antiTB drugs
  - reimplantation if no response: non-refluxing preferable w/ submucosal tunnel of > 2cm
    - must do cysto preop to find an area free from fibrosis and infection can be chosen for reimplant
    - inflammation usually only near UO, so is not a problem
  - ureteral dilation: q2-4weeks until stable → not recommended
  - psoas hitch
  - Boari flap
  - u-u, transureteroureterostomy

### **What are the indications for augmentation cystoplasty in GU TB?**

- intolerable frequency + pain, urgency, hematuria
  - small contracted hypertonic bladder
- capacity < 100cc
- deterioration of renal function

### **What are the contraindications to augmentation in GU TB?**

- enuresis ?
- incontinence ?
- psychiatric disturbance ?

### **Describe the workup required prior to augmentation cystoplasty for GU TB.**

- 4 weeks of intensive chemo prior to surgery
- flow rate
  - BN dilation in female if poor flow
  - TUIBN

### **What are the indications for permanent urinary diversion in GU TB?**

- hx of psychiatric disturbance/low intelligence (?)
- enuresis not related to small capacity (?)
- intolerable diurnal sx w/ incontinence not responded to chemotherapy

### **Why is a ureterosigmoid anastomosis not recommended?**

- incontinence often occurs

### **Why is the use of BCG as a vaccine controversial?**

- lasts only ~15 yrs
- some pts already infected and BCG won't work
- chance of complications: BCGitis, lupus vulgaris, lymphadenitis
- does not decrease chance of infection

## Chapter 21 Questions - GU TB.doc

### What is the etiologic agent of schistosomiasis?

- *S. haematobium*
  - worm pairs live in perivesical venous plexus

### Describe the life cycle of the schistosome. MSpCS

- Sexual reproduction
  - egg laying by adult worm pairs occurs in vesical and pelvic venules
    - 20% of eggs cross over into hollow viscera
      - ◆ excreted into urine or feces
    - 80% swept into microvasculature of lungs, liver, other sites
    - some eggs destroyed, others calcified and accumulate in viscera
  - eggs deposited into fresh water, shells break, and miracidia emerge
  - miracidia (product of sexual reproduction) migrates in fresh water to penetrate the snail
- Asexual reproduction
  - enter snail of *Bulinus* species and transform into sporocysts
  - sporocysts produce 20-40 daughter sporocysts, each producing 200-400 cercariae
  - cercariae leave daughter sporocysts, migrate to snail surface, and emerge into fresh water
  - cercariae penetrate unbroken skin of human and sloughs its tail → becomes a schistosomulum
    - die if they don't penetrate skin in a few hrs
  - congregate in lung for 4-7 days, in liver from 2<sup>nd</sup> week onward
    - adults worms do not produce significant disease in the host
  - adults pair off and go to sites to lay eggs

### Describe the pattern of oviposition in schistosomiasis.

- worm pairs distributed widely in pelvic and mesenteric venous plexuses
  - oviposition only mostly in pelvic lower urinary tract
- deposits eggs in groups: not singly

### Describe the bladder pathology in schistosomiasis.

- recent oviposition
  - perioval granulomatous inflammation: may be filled w/ viable eggs
  - bulky hyperemic polypoid masses projecting into lumen
- inactive urinary schistosomiasis
  - after adults worms have died
  - absence of viable worms in tissue/urine
  - sandy patches: flat, tan mucosal lesions of various depth
    - made of calcified eggs in dense fibrous tissue matrix
  - calcified bladder on x-ray

### What are the different patterns of egg accumulation in schistosomiasis?

- apicentric: begins and persists at dome
- basocentric: begins at base and trigone
- combined: randomly dispersed b/w based and apex

### What are the clinical stages of schistosomiasis?

- swimmer's itch (schistosomal dermatitis)
  - pruritic macular rash at site of cercarial penetration: 3-18 hrs after exposure
- acute schistosomiasis (aka Katayama fever)
  - fever, l/a, splenomegaly, eosinophilia, urticaria, other manifestations of serum-sickness
  - occurs 3-9 weeks after infection
- chronic urinary schistosomiasis
  - Chronic active phase
    - eggs deposited in tissue, traverse bladder and excreted
      - ◆ **hematuria and terminal dysuria**
    - enters quiescent period: sx decrease, egg deposition occurs at lower rate
    - silent obstructive uropathy occurs: hydroureteronephrosis
    - chronic/recurrent UTI w/ *Salmonella*
      - ◆ intermittent fever, anemia, splenomegaly

## Chapter 21 Questions - GU TB.doc

- nephrotic syndrome
- Chronic inactive phase
- viable eggs no longer detected in urine
- "sandy patches" present: flat, tan mucosal lesions of various depth
- fibrosis and sx due to obstructive uropathy

### How can one make the diagnosis of schistosomiasis?

- **hx: "Where have you been?"**
- urine: presence of terminally spined eggs
  - egg excretion peaks b/w 10am-2pm
- rectal or bladder mucosal bx: eggs seen on squash prep
- serologic testing
- radiologic testing: most important in chronic inactive schistosomiasis
  - Xray: calcified bladder (fetal head)
  - IVP: hydronephrosis, nonfunctioning kidney, ureteral stenosis, bladder and ureteral filling defects
    - mural calcification, tortuous ureters
  - VCUG: VUR
  - US: thickening of bladder wall, polypoid lesions of GU tract, hydro, calcific sandy patches
  - CT: obstructive uropathy and calcific lesions

### Describe the medical management of schistosomiasis.

- 2 drugs
  - praziquantel: interferes w/ ion transport in schistosome tegument
    - drug of choice: works against all schistosomal species
    - 40mg/kg PO x 2 doses
    - s/e: GI complaints, h/a, dizziness, fever
  - oxamniquine
    - effective only against *S. mansoni*
    - given over 2-3 days

### What are the indications for surgical treatment of schistosomiasis?

- complications that have not responded to medical treatment
- intractable bladder hemorrhage

### What is the prognosis of pts w/ schistosomiasis?

- generally good
  - determined by overall intensity and risk of reinfection
- pts that die are usually young, early stage disease, and heavy total egg burden
- prognosis good w/ newer drugs
- poor prognosis w/ bacterial superinfection
- transplant donor/recipient not contraindicated: need 2 mo of chemo prior

### How can one prevent infection w/ schistosomiasis?

- **no effective prophylactic drug**
- avoid infected streams, rivers, ponds, lakes

### What are the anatomic complications of *S. haematobium* infection?

- Urethra, Prostate, SV, BOO, Genitals
  - asymptomatic hematospermia
  - schistosomal cervicitis and vaginitis: dyspareunia
  - cervical stenosis
  - eggs/blood in ejaculate
  - **no documented case of fetal schistosomiasis**
- Bladder
  - polyposis
  - sandy patches
  - "contracted bladder"
    - occurs most frequently in later chronic active stage, when egg burdens are highest
    - sx: constant deep lower abdo/pelvic pain, LUTS, UI



## Chapter 21 Questions - GU TB.doc

- ulceration
  - 2 types: acute (necrotic polyp sloughs) or chronic
  - occur at posterior midsagittal line middle to upper
  - chronic deep bladder ulcers require partial cystectomy → fulgurization doesn't work
- hyperplasia/metaplasia
  - squamous or adenomatoid differentiation
  - epidermization
- cancer: SCC and adenoca
  - early onset (40-50 yrs), high frequency of SCC
    - ◆ SOU predisposes to UTI w/ bacteria that produce carcinogenic nitrosamines
  - 40% well-differentiated: good prognosis
  - nocturia, pain, hemorrhage
  - treat w/ radical anterior exenteration w/ urinary diversion
- UO obstruction
- UTI
  - bacteria produce carcinogenic nitrosamines
  - recurrent UTI from *Salmonella*
- Ureters and Kidneys
  - urolithiasis
  - ureteritis cystica calcinosa
  - **hydroureter and hydronephrosis: due to obstruction and ureteral hypotonia**
    - hydroureter usually occurs before hydronephrosis → hydronephrosis is final stage
  - ureteral obstruction
    - at UO, interstitial ureter, lower 1/3
    - most often caused by concentric/hemiconcentric polypoid lesions in interstitial and adjacent extravesical ureter
    - eggs perforate urothelium: allow urine into interstitium, causing spasm
    - ureteral hypotonia occurs
  - renal failure (SOU – schistosomal obstructive uropathy)
  - XGP
- Other
  - GI tract
    - sandy patches in rectum
    - schistosomal colonic polyposis
      - ◆ abdo pain, dysentery, finger clubbing, arthralgia, anemia, protein-losing enteropathy
      - ◆ requires cross-infection w/ *S. haematobium* and *S. mansoni*
    - schistosomal appendicitis
    - pulmonary involvement
  - CNS involvement
    - space-occupying lesion, myelitis, transverse myelitis
  - bilharziomas

### What are the different types of hydroureter seen in schistosomiasis?

- segmental
  - rarely any significant hydronephrosis
- tonic
  - dilated tortuous thick-walled trabeculated ureter w/ marked hypertrophy and active peristalsis
  - involves entire ureter proximal to obstructive lesion
- atonic
  - dilated tortuous thin-walled ureter w/o peristalsis and atrophic fibrotic ureteral muscle
  - involves entire ureter proximal to an obstruction

### What is the etiologic agent in genital filariasis?

- Lymphatic filariasis
  - *Wucheria bancrofti*
    - causes 90% of lymphatic filariasis
  - *Brugia malayi*
  - *Brugia timori*
- Non-lymphatic filariasis
  - *Loa*

## Chapter 21 Questions - GU TB.doc

- *Dietalonnema*
- *Dirofilaria*
- *Mansonella*
- *Onchocerca volvulus*: causes scrotal elephantiasis, African river blindness

### Describe the life cycle of the lymphatic filariae.

- cycle proceeds from human to mosquito and back
- Mosquito
  - female mosquito ingest microfilariae (first-stage larvae) in blood meal
  - larvae molt and go to mosquito salivary glands
  - infective larvae deposited on skin and penetrate mosquito bite
- Human
  - larvae proceed to lung and molt
  - *W. bancrofti* adult filariae live in periaortic, iliac, inguinal, and intrascrotal lymph vessels
  - female lays eggs

### Where is the distribution of lymphatic filariae?

- distributed in tropics and subtropics

### Describe the pathogenesis of lymphatic filariasis.

- Prepatent period
  - lymph vessels harbour worms → dilated
  - edema, vasodilation, inflammatory infiltration of tissues drained by lymphatics
- Early established infection
  - lesions persist and cause significant scarring
  - lesions at worms' nesting areas: epididymitis, orchitis, filarial lymphangitis, filarial abscess
    - worm death causes inflammatory response
  - exudative filarial lesions simulate abscesses → sterile
- Late infection
  - huge hydroceles and scrotal and penile elephantiasis
  - lymph vessels obstructed
  - elephant scrotum becomes secondarily infected

### What are the various forms of clinical lymphatic filariasis?

- asymptomatic
  - skin test reactivity
  - no microfilaremia, no clinical evidence of disease
- filarial fevers
  - episodic fevers, lymphangitis, epididymitis, transient edema, small hydroceles
  - typically amicrofilaremic
  - chronic hydrocele, chyluria, lymphedema, lymph scrotum
- chronic lesions
  - funiculoepididymitis
    - pain, lumpy or cordlike swelling, hydrocele
    - varicocele or thrombosis of pampiniform plexus
    - tx: antibiotics, surgical decompression or excision of filarial nodules, orchiectomy
    - orchitis is rare, sterility is rare
  - hydrocele
    - thick fibrous tunica w/ cholesterol or Ca deposits
      - ◆ calcification is so rare in hydrocele, that its presence suggests an infectious/filarial cause
    - milky or sediment-rich hydrocele fluid
  - scrotal and penile elephantiasis and lymph scrotum
    - excision w/ grafting
    - skin ulcers and sepsis
  - chyluria
    - dying worms cause lymphatic obstruction
    - rupture of lymphatic varix into collecting system
    - severe protein loss, hypoalbuminemia, anasarca
- tropical eosinophilia

## Chapter 21 Questions - GU TB.doc

- sustained peripheral eosinophilia
- responds to antifilarial drugs

### How does one make a diagnosis of filariasis?

- histologic finding of adult worms
- *Brugia* or *Wucheria* in blood, chylous urine, or hydrocele fluid
  - peak microfilaremia at midnight
- US observation of worms: "filarial dance sign"

### What is the medical management of filariasis?

- diethylcarbamazine (DEC): standard
  - 2 mg/kg/day PO TID x 2 weeks
  - s/e: N/V, h/a, F/C, arthralgias → due to dying filariae
  - can be used prophylactically: annual dose of 6mg/kg
- ivermectin
  - single dose 200-400 ug/kg
  - no effect on adult filariae
- albendazole
  - kills both adults and microfilariae

### What is the disease caused by *Onchocerca volvulus*?

- African river blindness
  - transmitted by black flies of *Simulium* species
  - may produce scrotal elephantiasis
  - tx w/ suramin or DEC or ivermectin

### What is the etiologic agent of hydatid disease?

- *Echinococcus granulosus*
  - definitive host: dog
  - intermediate host: sheep

### How do humans get hydatid disease?

- eating eggs excreted in dog feces

### How does hydatid disease present?

- pressure sx or flank pain
  - due to slow growth of hydatid cysts over years
- microscopic hematuria: rare

### What are the radiologic findings in hydatid disease?

- thick-walled fluid-filled spherical cyst
  - calcified cyst wall

### What is the treatment of hydatid disease?

- Medical
  - albendazole 400mg POD BID x 1-6mo
  - praziquantel: preoperatively
- Surgical
  - cyst removal
    - rupture of cysts may cause anaphylaxis

### Describe the pathology of amebiasis.

- renal abscess by *E. histolytica*
- liver abscess
- hematuria
- amebic ulceration of perineum





## Chapter 22

### • Fungal and Actinomycotic Infections of the GU System •

---

#### How can one classify fungal infections of the GU system?

- Opportunistic fungi
  - Candida
  - *Torulopsis glabrata*
  - Aspergillosis
  - Cryptococcosis
  - Phycomycosis (Mucormycosis, Zygomycosis)
- Primary fungal infections
  - Blastomycosis
  - Coccidiomycosis
  - Histoplasmosis
- Rare and unusual
  - Phaeohyphomycosis
  - *Fusarium*
  - Paracoccidioidomycosis
  - Penicillium
  - *Pseudallescheria boydii*
  - Rhinosporidiosis
  - Sporotrichosis
  - Tinea
  - Trichosporon
- Actinomycetes

#### What species of Candida usually cause GU infections?

- *C. albicans*: 74%
- *C. glabrata*: 8%
- *C. parapsilosis*: 7%
- *C. tropicalis*: 3%
- *C. lusitaniae*: 2% → some strains resistant to amphotericin B

#### What are the predisposing RF for Candida infection?

- IV catheter
- TPN
- diabetes
- antibiotic administration
- steroid therapy
- urine flow turbulence
- congenital anomalies
- neurogenic bladder
- malignancy
- malnutrition
- BCP, pregnancy, DM, abx: RF for Candidal vaginitis

#### What are the sx of candiduria?

- often asymptomatic
- LUTS
- flank pain/renal colic
  - fungus balls
- pyelo sx: flank pain, renal tenderness, fever
- oliguria/anuria: due to obstruction

## Chapter 22 Questions - Fungus.doc

- recurrent fever in immunocompromised pt

### How can one dx *Candida* infection?

- superficial infection: identification of fungus by smear or culture of wound exudate
- microscopic detection of *Candida* in vaginal exudates or by culture
- bladder: cysto demonstrates white patches on the bladder wall and areas of mucosal edema and erythema, hyphae in exudates
- upper tract: identification of fungus in urine, imaging studies (US, IVP, CT) that document obstruction

### What are the various manifestations of candiduria?

- superficial infection
  - around ileostomies/cutaneous pyelostomies: treat w/ topical antifungals
  - post-op wound infection: erythema and pustules in incision sites
- vaginitis
  - yellowish-white vaginal discharge and gray-white pseudomembranous exudate in vagina/vulva
  - pruritis
- genital infection
  - emphysematous cellulitis
  - epididymitis
- bladder/prostate infection
  - emphysematous cystitis
  - fungal bezoar
  - emphysematous cystitis/prostatitis
  - prostatic abscess
- upper tract infection
  - fungus balls → ureteral obstruction or renal pelvis obstruction
  - candidal pyocalix
  - perinephric abscess: fever, flank pain, +ve culture for *Candida*, abnormal US/CT
  - pyelo
  - papillary necrosis
- systemic candidal infection

### What is the management of Candidal vaginitis?

- send vaginal exudate for culture/microscopy
- nystatin intravaginally 10<sup>5</sup> u x 14 days
- topical imidazoles: butoconazole, clotrimazole, miconazole, terconazole, tioconazole
- PO fluconazole 150mg x 1: as effective as intravaginal clotrimazole
- chronic infections: ketoconazole 400mg OD x 14d followed by 100mg OD x 6/12
- boric acid powder 600mg in gelcap intravaginally x 2/52

### What is the management of Candidal infection of the upper tracts?

- identify fungus in urine
- imaging studies to document obstructive uropathy: US, IVP, CT
- NT
- IV amphotericin B
- irrigation of renal pelvis w/ amphotericin B

### What are the predisposing factors to Candidal infection of the upper tracts?

- candidal cystitis
- ileal conduit
- chronic neurogenic bladder

### What are the predisposing factors to candidemia in the surgical pt?

- renal failure
- hepatic dysfunction
- post-op shock
- ARDS
  - fungemia = failure of host resistance → ill pts should receive prophylactic antifungals

### What are the predisposing factors to development of renal candidal infection in infants?

## Chapter 22 Questions - Fungus.doc

- IV catheters
- broad-spectrum antibiotics
- prematurity
- low birth weight

### How can one diagnose GU Candida infection?

- Urine studies
  - microscopic examination: budding forms or pseudohyphae
    - pyuria and hematuria
    - fungal casts
  - culture from urine: CLED (cystine lactose electrolyte deficient) agar, blood agar, and Sabouraud's agar w/ dextrose
  - urinary candidal colony counts: high counts if renal infection vs. colonization
    - **cannot be used to differentiate colonization from local or invasive infection if indwelling catheter**
- Blood/serologic studies
  - no lab studies can indicate upper tract infection
  - persistence of positive Candida blood cultures
  - antibody response to candidal antigen: whole-cell agglutination, agar cell diffusion, latex agglutination, counterimmune electrophoresis, RIAs
- Imaging
  - cystogram, IVP, retrograde: filling defects
  - US: demonstration of fungal material
  - CT: mass lesion w/ less attenuation than stone

### Describe the general treatment for a GU candidal infection.

- Initial candiduria
  - single +ve culture: reassess if urine colony counts > 10000, otherwise observation may be appropriate
  - remove or change catheter (if present)
  - stop antibacterial antibiotics
  - **improve nutritional status**
  - remove TPN catheters if possible
- Reculture → if +ve:
  - assess for upper tract abnormalities: US, IVP, CT
    - filling defects: culture ureteral/renal urine → if +ve:
      - ◆ antifungal irrigation w/ NT or ureteral catheter w/ amphotericin B
      - ◆ perc removal of fungal bezoar
      - ◆ systemic amphotericin B, IV fluconazole
  - systemic manifestations: fever, WBC, other culture sites +ve?
    - systemic amphotericin B, IV fluconazole
  - otherwise: bladder irrigation w/ amphotericin B (50mg in 1000cc water/D5W at 1L/day), PO/IV fluconazole
    - persistent infection: systemic amphotericin B, IV fluconazole

### What are the potential systemic treatments for "local infection?"

- 5-FC > 100mg/kg/day PO
- fluconazole 100mg PO BID x 10d
- amphotericin B: 200-300mg IV daily
- liposomal amphotericin B
- imidazoles *miconazole* and *ketoconazole*: *poorly excreted by kidney, low urine concentrations*

### What is the gold standard for treatment of the pt w/ invasive or disseminated fungal infection?

- amphotericin B 6mg/kg

### What are the indications for nephrectomy in the setting of fungal infection?

- fungal abscess
- cellulitis
- diffuse parenchymal infection

### What are the GU manifestations of *Torulopsis glabrata*?

- voiding sx
- pyuria
- hematuria

## Chapter 22 Questions - Fungus.doc

- epididymitis
- pelvic abscess
- fungemia
- upper tract infection: flank pain, fever, WBC
- upper tract obstruction
- perirenal abscess

### What are the most common species of *Aspergillus* that cause GU infection?

- *A. fumigatus*
- *A. flavus*
- *A. niger*

### What are the various manifestations of *Aspergillus* infection?

- renal infection
  - renal aspergillomas/pseudotumours → in AIDS pts
  - abscesses
  - fungal vascular occlusion
    - renal infarcts
    - papillary necrosis secondary to vascular occlusion
- prostatic infection: BOO

### What is the treatment of renal aspergillomas?

- IV amphotericin B 1.5g x 3weeks + PO itraconazole 200 mg PO BID x 3 months
- in conjunction w/ surgical tx

### How can one diagnose *Aspergillus* infection?

- urine/tissue biopsy: identification w/ methenamine silver or PAS stain of the fungus
- blood cultures: usually –ve
- PCR amplification

### What is the treatment of *Aspergillus*?

- Medical
  - combination tx w/ 5-FC (8 g/day x 2/12) + amphi B
  - rifampin + amphi B
- Surgical
  - endourologic access: antegrade or retrograde
  - irrigation: NT or ureteral catheter
  - lavage and debulking: PCNL or via ureteropyeloscopy
  - re-irrigation
  - renal exploration, pyelotomy
  - nephrectomy

### What species of fungus causes cryptococcus GU infection?

- *Cryptococcus neoformans*

### What environment predisposes *Cryptococcus* to grow?

- live in any environment inhabited by birds (esp pigeons)
- found in old attics, buildings, and barn lofts

### Describe the sx of cryptococcus infection.

- asymptomatic pulmonary infection
- may develop into virulent respiratory infection that mimics severe pneumonia, TB, ca, or other fungal infections
- often self-limiting

### What pts are at increased risk of disseminated *Cryptococcus* infection?

- AIDS pts

### What is the primary site of extrapulmonary *Cryptococcus* infection?

- CNS is primary target of hematogenous spread
  - meningitis, meningoencephalitis, cryptococcoma



## Chapter 22 Questions - Fungus.doc

### How can one diagnose Cryptococcal infection?

- identification in urine, CSF, or other fluids: Sabouraud's glucose agar media
- direct examination of infected fluid w/ India ink
- identification in tissue w/ PAS or methenamine silver stain
- latex agglutination tests
- cryptococcal antigen in urine of AIDS pts

### What are the various GU manifestations of Cryptococcal infection?

- adrenal infection
- renal infection
  - cryptococcal pyelo
- prostatic infection
  - lesions vary from small chronic inflammatory changes to large granulomas w/ caseation
  - prostate is a reservoir for cryptococcus in AIDS pts after tx for cryptococcal meningitis
  - requires systemic tx w/ fluconazole
- genital infection
  - epididymitis: tx w/ orchiectomy and systemic amphotericin B, fluconazole, and 5-FU
  - penile infection: glans ulcer to large exophytic lesion → tx w/ excisional bx and systemic tx

### What genera make up the taxonomic family Mucoraceae?

- *Rhizopus*
- *Rhizomucor*
- *Mucor*
- *Absidia*

### What are the manifestations of Mucor infection?

- rhinocerebral infection: sinus, pharynx, meninges, brain
- pulmonary infection: associated w/ haem malignancies
- GI infection: in malnourished kids
- renal involvement
- cutaneous infection and inguinal abscesses
- disseminated zygomycosis: may involve pelvic organs

### What pt populations are at increased risk for developing disseminated mucormycosis?

- pts who require hemodialysis
- pts who receive deferoxamine

### Where is the fungus *Blastomyces dermatitidis* found?

- endemic in basins of the Ohio, Missouri, and Mississippi rivers
- Great Lakes region and Canada
- fungus has a predilection for moist soil w/ a high organic content

### What is the etiologic agent of South American blastomycosis?

- *Paracoccidioides brasiliensis*

### What is the natural hx of Blastomycosis infection?

- following inhalation, pulmonary infection may develop
  - often subclinical and self-limiting
- may disseminate by hematogenous or lymphatic route to extrapulmonary sites
  - skin, bones, GU system

### What conditions predispose pts to develop Blastomycosis?

- chronic steroid use
- hematologic malignancy
- solid tumour requiring cytotoxic or radiation therapy
- transplant recipient (solid organ or bone marrow)
- HIV +ve
- ESRD
- end-stage liver disease

## Chapter 22 Questions - Fungus.doc

- pregnancy

### What are the GU manifestations of Blastomycosis infection?

- GU involvement in 15-30% of pts w/ systemic disease
- prostatitis
  - LUTS, retention
  - prostatic abscess
- epididymitis
- adrenal infection
- systemic blastomycosis

### How can one diagnose Blastomycosis infection?

- CXR changes
- +ve Blastomyces skin test
- identification of fungus in urine, semen, or tissue
  - identify Blastomyces "broad neck" yeast forms in infected tissue
- serologic tests
  - Blastomyces A antigen

### What is the tx of Blastomyces infection?

- Disseminated disease: systemic amphotericin B 1-3g
- Mild/moderate nonmeningeal forms: itraconazole 400mg OD

### What fungus causes coccidioidomycosis?

- *Coccidioides immitis*

### Describe the natural habitat of coccidioidomycosis.

- indigenous to semiarid regions of Western US, Mexico, and Central and South America
- thrives in soil conditions that are inhibitory to competing organisms: high temperature and increased salinity

### What population groups are at increased risk of coccidioidomycosis?

- construction workers, farmers, archaeologists: exposed to dust

### Describe the natural hx and sx of coccidioidomycosis infection.

- asymptomatic and transient pulmonary infection
  - more virulent infection in some cases
  - high fever, cough, night sweats, or pleuritic pain
- "allergic" reaction to infection → erythema nodosum
  - aka "valley bumps" or "valley fever"
- <1% develop extrapulmonary manifestations
  - meninges, bone, skin, joints, soft tissue

### What are the RF for disseminated coccidioidomycosis?

- increased skin pigmentation
- pregnancy
- age < 5 or >50
- steroid use
- chemotherapy
- malignancy
- HIV+/AIDS

### What are the GU manifestations of coccidioidomycosis?

- kidney involvement (35-60%)
- adrenal involvement (16-32%)
- prostate involvement (6%)
  - BOO
  - granulomas
- bladder involvement
  - coccidioidal cystitis
- genital involvement

## Chapter 22 Questions - Fungus.doc

- scrotal swelling
- draining sinus
- epididymitis
- urethrocutaneous fistulae

### What are the renal radiographic findings of coccidioidomycosis?

- similar to TB: "moth-eaten" calyces, infundibular stenosis, renal calcification

### How can one diagnose coccidioidomycosis?

- Hx: pt travel to endemic areas, environmental hazards, immune suppression
- Serologic studies
- Culture draining sinuses
- tissue at bx stain w/ PAS or methenamine silver

### What is the tx of coccidioidomycosis?

- systemic antifungal tx: amphotericin B 1-1.5 mg/kg/d x 2-3mo
  - lipid formulations: less toxic
- ketoconazole x 1 year
- surgical resection of infected scrotal contents or prostate

### What population groups are at increased risk for developing histoplasmosis?

- individuals that work in chicken coops, infested caves, window sills, and other bird areas

### What is the natural hx of histoplasmosis?

- asymptomatic, self-limiting pulmonary infection
- may have cough, fever, hemoptysis
- if not tx, chronic pulmonary infection
- disseminated and virulent disease

### How can one diagnose histoplasmosis?

- CXR: small pulmonary granulomas and calcification
- +ve histoplasmin skin tests
- identification of *H. capsulatum* in tissue specimens by methenamine silver or Giemsa stain

### What are the GU manifestations of histoplasmosis?

- extrapulmonary: liver, spleen, LN
- adrenal
  - Addison's disease
- renal
- genital
  - superficial penile ulcers
  - epididymal histoplasmosis: surgical excision

### What is the tx of histoplasmosis?

- disseminated histoplasmosis: systemic tx w/ amphotericin B
  - imidazoles, IV miconazole, and PO ketoconazole → not good as primary tx
  - maintenance w/ amphotericin B or PO itraconazole to prevent relapse
  - immunocompromised pts: IV amphotericin B w/ long-term itraconazole
  - removal of infected organ

### Describe the natural hx of sporotrichosis.

- fungus gains entry via skin trauma
  - thorns, animal/insect bites
- induces chronic lymphocutaneous lesion
- dissemination : bones, joints, sinus, meninges

### Describe the urogenital manifestations of actinomyces infection.

- retroperitoneal abscess
- renal infections
- renal-colic fistula

## Chapter 22 Questions - Fungus.doc

- renal duodenal fistula
- intratesticular abscess
- ureteral obstruction

### How can one diagnose actinomyces infection?

- identification of sulfur granules in infected tissue
  - microcolonies of bacteria: develop yellow pigmentation

### What is the tx of actinomyces infection?

- Medical
  - penicillin IV 20 million units / day x 2 weeks
  - ampicillin PO 1500mg/day x 4 months
  - tetracycline, cipro, erythromycin
- Surgical
  - debridement of all infected tissue

### Describe the pharmacology of amphotericin B.

- polyene antifungal agent
- fungicidal and fungistatic properties
- binds to ergosterol component of the fungal cell membrane
  - results in disruption of internal cellular components to cause electrostatic flux
- $T_{1/2} = 15$  days

### What are the adverse effects of amphotericin B?

- rigors, chills, fever → tx w/ steroids 20mg IV given w/ ampho B
- pain, headache, convulsions, localized phlebitis, anemia, thrombocytopenia
- ototoxicity
- nephrotoxicity
- $K^+$  and  $Mg^{2+}$  depletion → can be corrected by supplementation, amiloride
- cardiac arrhythmias
- one congenital anomaly: microcephaly
- anaphylaxis: for liposomal amphotericin B
- fungal resistance to ampho B

### Describe the pharmacology of flucytosine.

- 5-FC is a fluorinated pyrimidine
- converted to 5-FU by cytosine deaminase
- readily absorbed by GI tract
- $T_{1/2} = 3-5$ hrs
- drug excreted unchanged by filtration
- can be cleared by dialysis

### What are the adverse effects of 5-FU?

- GI: N/V/D/enterocolitis
- LFT changes
- Haem: bone marrow depression, anemia, leukemia, thrombocytopenia, aplastic anemia
- headache, confusion
- **drug resistance in 10% of *C. albicans* → limits use in most GU fungal infections**

### Describe the pharmacology of the imidazoles and triazoles.

- imidazoles: **inhibit cytochrome P-450**
  - topical: clotrimazole, econazole, miconazole
  - oral: ketoconazole 400mg/day, increase to 800mg/day
    - absorbed from GI tract, peak concentration in 1-4 hrs
    - absorption limited if pt has achlorhydria or uses antacids: cimetidine or ranitidine
    - poor renal excretion → low urinary levels
  - IV: miconazole
- triazoles: greater affinity for fungal cytochrome P-450 than imidazoles
  - itraconazole 200mg PO TID x 3d, then 200-400mg OD
    - lipophilic

## Chapter 22 Questions - Fungus.doc

- absorption enhanced if take w/ food
- works against *Aspergilla*, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Sporotrichosis*
- fluconazole 200mg PO OD x 7d
- PO administration not affected by food
- water soluble
- efficacious in tx of *Candida*, *Torulopsis*, *Cryptococcus*

### What important drug interactions occur involving the azoles and other commonly used medications?

- Decreased plasma concentration of azole
  - antacids: ketoconazole, itraconazole
  - H<sub>2</sub>-receptor antagonists: ketoconazole, itraconazole
  - sucralfate: (ketoconazole) → maybe
- Increased plasma concentration of azole
  - isoniazid: ketoconazole
  - phenytoin: ketoconazole, itraconazole
  - rifampin: ketoconazole, itraconazole, (fluconazole)
- Increased plasma concentration of coadministered drug
  - warfarin: (ketoconazole, itraconazole, fluconazole)
  - cyclosporin: ketoconazole, (fluconazole, itraconazole)
  - digoxin: (itraconazole)
  - phenytoin: ketoconazole, fluconazole, (itraconazole)
  - sulfonylurea drugs (esp tolbutamide): (ketoconazole, itraconazole, fluconazole)
  - terfenadine: ketoconazole, itraconazole
  - astemizole: ketoconazole,, itraconazole

### What are the common or serious adverse effects of systemic antifungals?

- ketoconazole
  - GI: N/V, abdo pain, anorexia
  - Skin: rash
  - Liver: elevation of serum triglycerides and abnormal LFTs
  - Bone marrow: none
  - Kidney: none
  - Endocrine: adrenal insufficiency, decreased libido, ED, gynecomastia, menstrual irregularities → affects androgen metabolism
  - Other: headache, fever, chills
- itraconazole
  - GI: N/V
  - Skin: pruritis, rash
  - Liver: elevation of LFTs, hepatitis
  - Bone marrow: none
  - Kidney: none
  - Endocrine: hypokalemia, hypertension, edema, ED
  - Other: headache, dizziness
- fluconazole
  - GI: N/V
  - Skin: rash, possible SJS
  - Liver: elevation of LFTs, hepatitis
  - Bone marrow: none
  - Kidney: none
  - Endocrine: none
  - Other: headache, seizure
- miconazole
  - GI: N/V
  - Skin: none
  - Liver: none
  - Bone marrow: anemia, leukopenia, thrombocytosis or thrombocytopenia
  - Kidney: none
  - Endocrine: hyperlipidemia, hyponatremia
  - Other: phlebitis, fever, psychosis

## Chapter 22 Questions - Fungus.doc

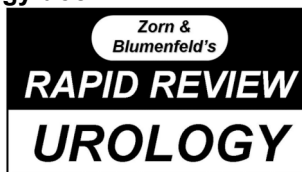
- flucytosine
  - GI: N/V, abdo pain, diarrhea
  - Skin: rash
  - Liver: elevation of LFTs, hepatitis
  - Bone marrow: anemia, leukopenia, thrombocytopenia
  - Kidney: none
  - Endocrine: none
  - Other: headache, confusion
- amphotericin B
  - GI: N/V, anorexia
  - Skin: none
  - Liver: none
  - Bone marrow: anemia
  - Kidney: azotemia, RTA, hypokalemia, hypomagnesemia
  - Endocrine: none
  - Other: headache, fever, chills, thrombophlebitis

### What are the other treatment modalities for fungal infections?

- alkalization
  - ideal growth pH ranges from 5.1-6.4 (similar to urinary pH)
- allylamine (terinafine and naftidine) → ergosterol biosynthetic inhibitors w/ antifungal activity
- transfer factor: derived from lymphocyte lysates
- GSF

### Describe the medical tx (including doses) for each major GU fungal infection.

- Aspergillosis
  - renal or prostate: amphotericin B 1.5mg/kg/day IV + 40ml/hr irrigation x 6-18wk + itraconazole 200mg PO BID x 1yr
- Blastomycosis
  - prostate: ketoconazole 400mg PO OD x 1mo + amphotericin B 1-3g IV q3/12
  - epididymitis: ketoconazole 400mg PO OD x 1yr
- Candida and Torulopsis
  - balanitis: nystatin cream or fluconazole 150mg PO x1
  - vaginitis: nystatin intravaginally x 14d
  - bladder: fluconazole 150mg PO OD x 7d
  - kidney: amphotericin B 1g IV + 40ml/hr irrigation
  - prostate: fluconazole 20mg PO BID x 6 weeks
- Coccidioidomycosis
  - kidney: amphotericin B 2g IV
  - prostate: amphotericin B 2.5g IV x 4mo
  - bladder: amphotericin B 2g IV + ketoconazole 200mg PO OD x 1 yr
- Cryptococcosis
  - prostate: amphotericin B 1-3.4g total dose IV or flucytosine 100-150mg/kg/day x 4-6wk or fluconazole 200-600mg PO OD x 2-6/12
- Histoplasmosis
  - renal: amphotericin B
  - prostate: ketoconazole 600mg/day or itraconazole 200mg/day
- Mucormycosis
  - renal: amphotericin B > 1g IV x 1mo



## **Chapter 23**

### **• Physiology and Pharmacology of the Bladder and Urethra •**

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#### **Describe the anatomy of the bladder outlet.**

- bladder base
  - superficial longitudinal layer beneath trigone
  - deep layer continuous w/ trigone
- urethra
  - 4 parts in men: prostatic, membranous, bulbous, penile
- EUS

#### **What is the difference b/w the sphincter in men vs. women?**

- women: urethra composed of tissues that aid continence, rather than distinct and visible sphincter
  - density of adrenergic innervation at BN less compared to men
- men: complete and competent ring of smooth muscle at the BN
  - large amount of sympathetic noradrenergic innervation that contract BN during ejaculation

#### **What is Laplace's law?**

- tension in the wall of a container is proportional to the a radius at any given pressure
- $T = P \times R/2$

#### **How does injury, obstruction, or denervation affect human bladder composition?**

- increases collagen content

#### **What is the definition of bladder compliance?**

- change in volume relative to the corresponding change in intravesical pressure
  - $C = \Delta V / \Delta P$
- when collagen levels increase, compliance falls
  - increases w/ injury, obstruction, or denervation

#### **What is the mechanism by which the detrusor thins to allow for increased volume?**

- rearrangement of the muscle bundles from top-to-bottom to side-to-side configuration
- alteration of collagen coil structure: become extended, longer, taut, and assume an orientation so that fibers become oriented parallel to the lumen

#### **Why does a low voiding pressure in a woman not imply impaired detrusor contractility?**

- very little outlet resistance
- small amount of Pdet needed to achieve work necessary to empty bladder

#### **What are the functions of the bladder?**

- must store a socially adequate volume of urine at low compliance
- protect smooth muscle and nerves from exposure to urine: maintains osmotic gradient b/w plasma and urine
- synchronous activation of smooth muscle for coordinated emptying

#### **Describe the cell characteristics of smooth muscle.**

- small spindle shaped cells w/ central nucleus
  - not arranged in regular sarcomere pattern
- several hundred um long w/ 5-6 um diameter
- linked together at specific junctions
- contain actin and myosin fibers
- contain intermediate filaments

#### **What are the counterparts to Z lines of skeletal muscle that exist in smooth muscle?**

## Chapter 23 Questions - Bladder physiology.doc

- dense bodies
  - distributed throughout the cytoplasm
  - attachments for both thin actin and intermediate filaments
  - cross fibers obliquely in a lattice-like arrangement

### Compare and contrast the properties of skeletal vs. smooth muscle.

- skeletal
  - cell characteristics: very long, many nuclei → 30cm x 100um
  - sarcomere pattern, visible striations
  - no intermediate filaments
  - somatic innervation
  - contraction via disinhibition of tropomyosin
  - regulation of Ca via T tubule
- smooth
  - cell characteristics: spindle-shaped cells, single nucleus → 200um x 5um
  - no sarcomere pattern, no visible striations
  - many intermediate filaments
  - autonomic innervation
  - contraction via active phosphorylation of myosin
  - regulation of Ca via Ca channels, internal stores
  - more adaptable than skeletal muscle: can adjust its length over wider range
    - smooth muscle can shorten by > 2/3 of its original length
  - contractile response slower and longer lasting: due to slowness w/ which smooth muscle can hydrolyze ATP
    - 30X longer to contract and relax than does skeletal muscle
    - maintains same contractile tension for prolonged periods at < 1% of the energy cost
  - poor electrical coupling b/w smooth muscle cells: no fused tetanic contractions

### Describe the mechanism by which smooth muscle contraction occurs.

- resting membrane potential of -50 to -60 mV
- ACh interacts w/ M3 muscarinic receptors and activates PLC via a G protein
- PLC cleaves  $PIP_2 \rightarrow IP_3$  and DAG
  - $IP_3$  elicits release of calcium from internal stores (sarcoplasmic reticulum)
  - DAG interacts w/ L-type calcium channel in cell membrane, allowing Ca influx
  - ATP acting through P2X purinoceptors open nonselective cation channels, leading to further depolarization
- rise in intracellular calcium
- Ca binds to calmodulin, activating it
- Ca-calmodulin complex activates myosin light chain kinase (MLCK)
- MLCK phosphorylates myosin type II light chain, allowing myosin to interact w/ actin of the thin filaments
- ATPase activity of myosin heads switched on
- cross-bridge cycling initiated
- detrusor muscle contracts and shortens by interaction b/w thin and thick filaments
- membrane potential repolarized by the effect of intracellular Ca
  - high levels of intracellular Ca block L-type Ca channels
  - opening of K channels: maxi-K and  $K_{ATP}$  channels

### What different ion channels exist in the smooth muscle cell membrane?

- several different K channels
  - delayed rectifier
  - transient outward channels
  - large and small Ca-activated K channels
  - K channel opened by reduced intracellular ATP
- L-type Ca channel
- nonspecific cation channel → linked to P2X receptor

### Why is the contractile response of smooth muscle slower and longer lasting than that of skeletal muscle?

- smooth muscle is slow to hydrolyze ATP during the contractile process

How does smooth muscle ion activity change during bladder filling?

- as bladder fills, myocytes are stretched, activating nonselective cation channels, allowing some depolarization
  - poor coupling b/w cells prevents synchronous activation of smooth muscle during bladder filling



## Chapter 23 Questions - Bladder physiology.doc

- if stretch is significant, activation of cation channels may depolarize the cell
- whole contraction generally requires parasympathetic stimulation
- when the membrane is sufficiently depolarized, L-type Ca channels open and Ca channels in the SR open, flooding the cell w/ Ca and resulting in an AP

### What factors affect smooth muscle tone in the bladder?

- Intrinsic
  - response to stretch
  - local metabolites
  - locally secreted agents
  - temperature
- Extrinsic
  - activity in the autonomic nerves
  - circulating hormones

### What is *stress relaxation*?

- if smooth muscle is stretched, there is increase in tension immediately after, followed by progressive relaxation
  - unique to smooth muscle

### What are the main constituents of bladder wall stroma?

- collagen and elastin, in matrix composed of proteoglycans
  - main cells: fibroblasts
  - collagen: types I, III, and IV → I and III are the 2 major types
    - most is found in the connective tissue outside of the muscle bundles
  - elastin: amorphous structures made of elastin and a microfibrillar component
    - sparse in the bladder when compared w/ collagen
  - bladder matrix
    - gel of proteoglycans (glycoproteins w/ covalently attached GAGs) and water

### How is collagen altered in poorly compliant vs. normal bladders?

- ratio of connective tissue to smooth muscle significantly increased in poorly compliant bladders
  - smooth muscle also decreases relative to collagen with aging
- ratio of type III to type I collagen significantly elevated

### How is blood flow to the urothelium affected by bladder filling?

- blood flow reduced by distention
  - **intramural tension is the principal determinant of blood flow in the bladder wall**
  - blood vessels must be able to change length considerably

### What are the different layers of the bladder urothelium?

- Superficial layer
  - GAG layer
  - uroplakin plaques and discoidal vesicles
  - zona occludens
- Muscle layer
  - umbrella cell stratum → largest epithelial cells in the body
  - intermediate cell stratum → superficial to basal cells, 100-200µm in diameter, polyhedral
  - basal cell stratum → germinal in nature, 5-10µm in diameter
- Basal lamina

### What are the potential roles of the GAG layer?

- bacterial antiadherence
- prevention of formation and attachments of particulates / stone formation
- prevention of urothelial damage by large macromolecules
- ?controversy → epithelial barrier between urine and plasma

### What problems exist with the theory of the GAG layer being the urothelial plasma barrier?

- GAG layer does not prevent small molecules (ex: amiloride) from reaching the sodium channels on the umbrella cells
- nystatin can reach the urothelium
- first resistive barrier found on entry into the cell

## Chapter 23 Questions - Bladder physiology.doc

- hydrolytic and proteolytic agents do not alter ability of protamine to increase the urothelial permeability

### How does protamine sulfate affect the urothelium?

- increases apical membrane permeability to both monovalent cations and anions
  - prolonged exposure > 15min is poorly reversible
- reversed w/ PPS, HA, heparin (best of the 3)

### What are the cellular features of the umbrella cells?

- ability to increase and decrease their surface area considerably
- multinucleate
- asymmetrical apical surface membrane
  - outer leaflet: protein plaques (urolakin type I) and lipid
  - inner leaflet: lipid only
- cells maintain extremely high gradient b/w plasma and urine re: water, urea, K, osmolality, pH
- cover several intermediate cells
  - may have stem that extends to lamina propria of the urothelium

### What are the potential theories regarding how umbrella cells change their surface area w/ filling?

- large # of subapical discoid vesicles w/ asymmetrical membrane structure
- infoldings of membrane that stretch out and disappear

### What is the primary function of the urolakin proteins?

- part of the primary plasma-urine barrier

### What are the determinants of urothelial permeability?

- passive diffusion
  - passive permeability to most substances in blood or urine
- osmotically driven diffusion
  - urothelium maintains osmotic gradient b/w plasma and urine
  - increased permeability in inflammatory conditions → basis for K sensitivity test
    - K penetrates urothelium in inflamed bladder and causes pain by activation of bladder afferents
- active transport
  - active Na transport across the urothelium, transported out at basolateral membrane by Na-K exchanger
    - causes net -ve charge in cell
- inertness of membrane to the solutes to which it is exposed

### What ion channels exist in the umbrella cells?

- amiloride-sensitive sodium channels on apical surface → role unknown
- Na-K exchanger on basolateral membrane

### How are the muscular layers arranged in the urethra?

- thick inner longitudinal layer
- thin outer circular layer
  - gathered into small bundles and linked to each other by adherens-type junctions → no gap junctions

### What is the rhabdosphincter?

- striated muscle in the walls of the male and female urethra → separate from the periurethral skeletal muscle of pelvic floor
  - male: extends from bladder base and anterior prostate to full length of membranous urethra
  - female: from proximal urethra distally
- horseshoe shaped
  - **striated components are deficient posteriorly**

### How does the arrangement of muscle forming the distal sphincter differ in the female?

- female has attenuated striated sphincter mechanism
- additional muscle structures → compressor urethrae and urethrovaginal sphincter

### How is urinary continence maintained during IAP elevations in women?

- passive transmission of pressure to proximal urethra
- guarding reflex: active contraction of striated muscle of the EUS

## Chapter 23 Questions - Bladder physiology.doc

- hammock hypothesis: pressure transmitted through proximal urethra presses anterior wall against posterior wall
  - posterior wall remains rigid if adequate support
  - pubourethral attachments actively change BN position and proximal urethra during voiding
  - compresses urethra against pubis during filling and straining

### What different types of muscle fibers exist in the urethral sphincter?

- striated muscles
  - slow-type
  - twitch-type
    - slow-twitch → in muscles that require sustained tension, recruited and fatigue slowly
      - ◆ contain slow isoforms of myosin ATPase
    - fast-twitch → add to sphincter tone rapidly, fatigue rapidly, anaerobic
      - ◆ rapid bursts of contractile force
      - ◆ rich in myosin ATPase that catalyzes actin-myosin interaction
- smooth muscles
  - noradrenergic innervation

### What is the composition of the male and female EUS?

- periurethral striated muscle of the pelvic floor
  - contains fast- and slow-twitch types
- striated muscle of distal sphincter (rhabdosphincter)
  - mostly slow-twitch
  - male: 35% fast-twitch, 65% slow-twitch
  - female: 13% fast-twitch, 87% slow-twitch
- smooth muscle

### Describe the innervation of the bladder.

- Sympathetic: induce bladder relaxation and BN contraction
  - efferent motoneuron passes as preganglionic fiber through ventral root of spinal nerve and white ramus to reach sympathetic trunk ganglion
    - synapses w/ postganglionic neurons of same level, passes to another level within trunk to synapse (via gray ramus), or passes through ganglion intact to synapse within prevertebral or terminal ganglion
    - sympathetic fibers run through lumbar splanchnic nerves (L1-4)
      - ◆ L1 and L2: to inferior mesenteric plexus
      - ◆ L3 and L4: to superior hypogastric plexus
      - ◆ some pass down to S2-3 level, pass through sacral splanchnic nerves to inferior hypogastric (pelvic) plexus directly
    - run through hypogastric nerves to inferior hypogastric (pelvic) plexus
    - synapse w/ postganglionic neurons in inferior hypogastric (pelvic) plexus, join w/ parasympathetics
- Parasympathetic: induce bladder contraction and BN relaxation
  - efferent motor neurons only
    - preganglionic fibers arise from neurons in lateral part of sacral intermediate gray matter called **SPN (sacral parasympathetic nucleus)** → release ACh
    - parasympathetic fibers pass as preganglionic neurons from sacral cord through ventral root to sacral plexus → pelvic splanchnic nerves (nervi erigentes) to inferior hypogastric plexus to ganglia within bladder wall (vesical plexus)
    - some fibers continue on past prostate as cavernous nerves to supply erection
- Somatic
  - EUS motoneurons located along the lateral border of the ventral horn = **Onuf's nucleus**
    - pass through S2-4 to pudendal nerve to EUS

### Describe the afferent pathways from the bladder.

- cell bodies of afferent sensory neurons lie in DRG
  - monitor the volume of the bladder and the amplitude of bladder contractions
  - neuron passes w/o synapse from viscus to spinal cord through white ramus
- afferent axons in pelvic splanchnic, sacral splanchnic, lumbar splanchnic, hypogastric, and pudendal nerves
  - **travel caudally through Lissauer's tract in cord**

### What are the different types of bladder afferent nerves?

- A-delta: sense bladder fullness → finely myelinated

## Chapter 23 Questions - Bladder physiology.doc

- in smooth muscle
- if inflamed, discharge at lower pressure threshold
- C fiber: sense stretch, overdistension, irritants → unmyelinated
  - in mucosa and mucosa muscularis
  - if inflamed, increase discharge at lower threshold, and becomes mechanosensitive

### What reflex circuitry is active during the storage phase of the bladder?

- bladder-to-sympathetic reflex
  - contracts bladder outlet
  - inhibits detrusor contractions
  - inhibits ganglia
- bladder-to-EUS reflex ("guarding" reflex)
  - pudendal motoneurons activated by bladder afferent input
- sphincter-to-bladder reflex
  - contributes to suppression of bladder activity during storage
  - EUS stimulation will stimulate interneurons that suppress detrusor contraction

### What reflex circuitry is active during the emptying phase of the bladder?

- supraspinal pathways necessary to turn off sphincter and urethral guarding reflexes to allow for efficient emptying
  - afferent pathways terminate on second-order interneurons that relay info to the brain
  - EUS afferent terminals in superficial layers of the dorsal horn (and at base: laminae V, VI, VII, X)
  - glutamic acid: primary excitatory NT, GABA and glycine are primary inhibitory NTs
- urethra-to-bladder reflex
  - activity in afferent urethral nerves stimulate parasympathetic outflow to detrusor and inhibit sympathetic flow
  - via spinal pathway as well as supraspinal pathway through PMC (pontine micturition centre) and periaqueductal grey matter (PAG)
  - **SUI can cause UII**

### Describe the events that occur during the micturition cycle.

- Storage
  - bladder accommodation during filling: primarily passive phenomenon depending on elastic and viscoelastic properties of bladder wall
  - increase in outlet resistance w/ filling due to guarding reflex
  - inhibition of bladder contractility via direct inhibition of parasympathetics by sympathetics
  - sympathetic stimulation of  $\alpha$  receptors in smooth sphincter: increased resistance at BN
  - sympathetic stimulation of  $\beta$  receptors in detrusor: decrease in bladder wall tension
- Voiding
  - can switch to voiding phase voluntarily or involuntarily (reflexly)
  - increased afferent firing reverses the pattern of efferent outflow
    - inhibition of spinal somatic and sympathetic reflexes via supraspinal pathway through PMC and PAG
    - activation of vesical parasympathetic pathways
  - relaxation of EUS and bladder outlet: via cessation of sympathetic reflexes, +/- release of NO
  - coordinated parasympathetic contraction of bladder smooth muscle w/ funneling of BN

### What is Barrington's nucleus?

- pontine micturition center = M region
  - in dorsal pontine tegmentum
  - some neurons in PMC also send out axon collaterals to PVN and PAG
  - pass down to sacral PGN

### Why do L-sided hemiplegics complain more often of urgency?

- **micturition controlled by R side of brain**
  - frontal cortex and anterior cingulate gyrus
  - PMC on R side
- voluntary voiding dependent on connections b/w frontal cortex and septal/preoptic region of hypothalamus

### What is the hypothesis of mechanism of action of sacral neuromodulation?

- electrical stimulation of afferent axons in spinal roots modulate voiding and continence reflex pathways
  - instability suppressed by direct inhibition of bladder parasympathetic preganglionic neurons or interneurons that normally contract bladder and relax outlet

## Chapter 23 Questions - Bladder physiology.doc

- retention and dysfunction voiding suppressed by inhibition of guarding reflex that normally stimulates outlet contraction

### What is the bladder ice-water test?

- neonatal pathways for bladder instability do not disappear w/ growth → **increasing cerebral maturation actively inhibits them**
- bladder ice-water test unmasks primitive neonatal micturition reflexes
  - instill 100cc ice-cold saline quickly into bladder
  - normal adult will sense cold, but maintains stable bladder
  - infants and neuropathic pts develop involuntary contractions: +ve until age 4 usually

### What neurotransmitters are involved in bladder contraction and relaxation?

- Peripheral
  - Voiding
    - Cholinergic
      - ◆ M1, M2, M3 receptors in bladder: 5 types exist based on cloning, 4 based on pharmacology (M1-5)
      - ◆ M2 receptors predominate in number: coactivation may enhance M3 response
        - ◆ may inhibit adenylate cyclase, inactivate K channels, and activate nonspecific cation channels
      - ◆ M3 receptors mediate cholinergic contractions: via IP<sub>3</sub> hydrolysis and release of intracellular Ca
        - ◆ plays key roles in salivary secretion, pupillary constriction, and detrusor contractions
      - ◆ also present prejunctionally on cholinergic nerve terminals
        - ◆ M1 activates ACh release, M2/M4 inhibit release
    - NO
      - ◆ major inhibitory NT mediating relaxation of urethral smooth muscle during voiding
      - ◆ NO also involved in controlling bladder afferent activity
        - ◆ can be released by the urothelium, especially during inflammation
      - ◆ intravesical NO can suppress instability
      - ◆ involved in inflammatory and pain pathways, also part of the sensory signalling mechanisms of urothelium
    - PGs
      - ◆ PGF<sub>2α</sub>, PGE, PGE<sub>2</sub> contract detrusor (in decreasing potency)
    - Endothelins
      - ◆ contract isolated strips of bladder muscle
  - Storage
    - Adrenergic
      - ◆ β-adrenergic
        - ◆ stimulation of β<sub>2</sub>- and β<sub>3</sub>-adrenergic receptors in detrusor directly relaxes smooth muscle
        - ◆ mediated through stimulation of adenyl cyclase and formation of cAMP
          - ?specific isoform of PDE present in bladder vs. penis
      - ◆ α-adrenergic
        - ◆ α stimulation not very prominent in bladder, more important in urethral function
          - under pathologic conditions, R density can increase to that normal NE-induced response converted from relaxation to contraction
        - ◆ α<sub>2</sub> subtype predominate in female animals, α<sub>1</sub> subtype predominate in males
        - ◆ α-agonists produce a rise in intraurethral pressure → prevented by α-blocking agents
        - ◆ α<sub>1A</sub> adrenoceptor is major subtype in the prostate and urethra
        - ◆ α<sub>1A</sub>, α<sub>1B</sub>, α<sub>1D</sub> all present in blood vessels
    - Purinergic
      - ◆ contribute to parasympathetic/cholinergic stimulation, may play a role in pathologic conditions
        - ◆ involved in mechanosensory signalling in the bladder
      - ◆ ATP acts on 2 families of purinergic receptors
        - ◆ ion channel family: P<sub>2</sub>X → 7 subtypes
        - ◆ G protein-coupled receptor family: P<sub>2</sub>Y → 8 subtypes
      - ◆ intravesical ATP activates bladder afferents to enhance reflex activity
      - ◆ ATP acts via P<sub>2</sub>Y receptors in smooth muscle to suppress cholinergic contractions
      - ◆ adenosine can depress parasympathetic nerve evoked bladder contractions via inhibitory R in parasympathetic ganglia
    - Serotonin
      - ◆ 5-HT<sub>2</sub> and possibly 5-HT<sub>3</sub> agonists contract the urethra
    - Steroids and hormones
      - ◆ sex steroids do not affect bladder contractility: modulate R and influence growth of bladder tissues

## Chapter 23 Questions - Bladder physiology.doc

- ◆ estrogens increase adrenergic R in the urethra
- ◆ progesterone increases electrical and cholinergic contractions of the bladder
- ◆ PTH-related peptide (PTHrp): made by bladder muscle, causes detrusor relaxation
- Afferent neuropeptides
  - tachykinins
    - ◆ substance P, neurokinin A, neurokinin B
      - ◆ 3 receptors: NK1, NK2, NK3
    - ◆ release from capsaicin-sensitive sensory C fibers in response to irritation
    - ◆ cause vasodilation, stimulate bladder contractions, and increase excitability during bladder filling
    - ◆ NK1 blockers increase bladder capacity
  - CGRP (calcitonin gene related peptide): relaxes smooth muscle and produces vasodilation
  - VIP: inhibits spontaneous contractions in normal cats
- Spinal
  - Glutamatergic, GABAergic/glycinergic
    - glutamic acid = excitatory NT in afferent limb of voiding reflex
    - GABA, glycine = inhibitory NT, increases bladder capacity and decreases voiding pressure
  - Adrenergic: excitatory and inhibitory influences
    - intrathecal  $\alpha_1$ -blocker decreases amplitude of bladder contractions and inhibits voiding
    - intrathecal  $\alpha_1$ -agonist increases bladder pressure and facilitates voiding
    - conflicting role of  $\alpha_2$  receptors
  - Serotonin
    - activation of 5-HT R in cord inhibits bladder contractions
    - duloxetine (SNRI) increases neural activity of both urethral sphincter and bladder
  - Purinergic
    - inhibitory action of adenosine A1 agonist
  - Opioids
    - inhibitory action on reflex pathways in cord
- Supraspinal
  - glutamatergic: excitatory
  - GABAergic: inhibitory
  - cholinergic: excitatory
  - dopaminergic: inhibitory (D1-like effects) and excitatory effects (D2-like effects)
  - opioid peptides: inhibitory

### What is darifenacin?

- M3-receptor subtype selective anticholinergic
- not tissue selective

### How do oxybutynin and tolterodine compare in terms of efficacy and selectivity?

- **tolterodine has less activity on muscarinic R in salivary gland than in bladder**
  - not an M3 subtype-selective antagonist: organ specificity for the bladder
- overall efficacy similar
- side effects less w/ tolterodine

### What are capsaicin and resinaferatoxin, and how do they work?

- vanilloids that stimulate and desensitize unmyelinated C fibers to produce pain and release neuropeptides
  - activate sensory fibers through ion channel: **vanilloid receptor subtype 1 (VR1)**
  - nonselective cation channel, limited selectivity for calcium
  - induce analgesia via downregulation of substance P, upregulation of NOS, VIP, galanin
- capsaicin 1-2mM x 30min
  - irritant and algogenic compound from hot red peppers
  - highly selective effects on subset of sensory neurons: polymodal R and warm thermoreceptors
  - opens cation-selective ion channel VR1 (vanilloid receptor subtype 1), allowing  $\text{Ca}^{2+}/\text{Na}^{+}$  influx that depolarizes neuronal pain fibers
  - antinociceptive and anti-inflammatory action after initial algescic effect
  - lack of systemic s/e, no long-term adverse effects
  - motor fibers not affected
- resinaferatoxin (RTX) is ultrapotent analogue
  - from cactus-like plant *Euphorbia resinifera*
  - is a vanilloid: ultrapotent analogue of capsaicin → 1000X more potent w/ minimal initial excitatory effect

## Chapter 23 Questions - Bladder physiology.doc

- currents induced by resinaferatoxin develop slowly and are more sustained
  - causes desensitization without previous stimulation
- both meds should only affect small unmyelinated afferent C fibers
  - micturition reflex stimulated by A-delta myelinated fibers should not be affected
- difference due to receptor gating → RTX opens channel after initial delay, then provokes persistent currents
- slowly increasing intracellular calcium levels not enough to cause AP formation
- may inhibit TTX-insensitive sodium channels involved in AP generation

### How do potassium channel openers affect smooth muscle activity?

- stimulate movement of K out of cell, resulting in hyperpolarization
- reduce spontaneous contractile activity
  - ex: cromakalim, pinacidil

### What types of K channels have been identified in the detrusor?

- ATP-sensitive
- Ca-dependent small conductance
- Ca-dependent large conductance

### What is duloxetine and how does it work?

- combined NE and serotonin reuptake inhibitor (SNRI)
- increases activity of urethral sphincter and decreases bladder activity

### How does SCI result in bladder instability?

- disrupts normal supraspinal pathways that control urine storage and release
  - spinal shock + retention x weeks
  - hyperreflexia after this
- hyperreflexia due to spinal voiding reflex that emerges in response to reorganization of synaptic connections in cord
  - bladder afferents that are normally unresponsive to low Pves become more sensitive, leading to instability
- after SCI, **capsaicin-sensitive C fiber-mediated reflex develops (normally A-delta fibers)**
  - increased mechanosensitivity of C fibers

### How does BOO result in bladder instability?

- smooth muscle cell hypertrophy, decrease in myofilaments, damaged mitochondria, damage to autonomic nerves
  - axonal degeneration by day 7
- bladder enlarges, increase in muscle cell size
- increased density of afferent and efferent nerve fibers
- absence of gap junctions b/w cells, patchy denervation
- **results in denervation supersensitivity w/ increased contractile response** to cholinergic agonist
- association b/w htn and bladder instability in men w/ BPH

### How does inflammation result in bladder instability?

- **reduction in thresholds for bladder afferents**
- inflammation accompanied by neuroplasticity in sensory nerves supplying the bladder
- reduced K channels

### Does aging result in decreased detrusor contractility?

- not certain
  - most studies have not shown a significant difference in contraction response to cholinergic agonists w/ age
  - detrusor response to  $\beta$ -adrenergic stimulation decreased in old rats

### How do sex steroids affect bladder function?

- estrogen may affect voiding function
  - some neurons in cord contain estrogen receptors
  - decreased estrogen may decrease contractile response, or may decrease sensitivity to stimulation
  - estrogen increases adrenergic R in urethra



## Chapter 24

### • Pathophysiology and Categorization of Voiding Dysfunction •

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#### **What functions are required for bladder filling and storage?**

- accommodation of increasing volumes at low pressures w/ appropriate sensation
- bladder outlet closed at rest and w/ increased IAP
- absence of involuntary contractions

#### **What functions are required for bladder emptying?**

- coordinated contraction
- lowering of resistance at BN
- absence of anatomic obstruction

#### **Describe the functional classification of voiding dysfunction.**

- failure to store
  - due to bladder
    - involuntary contraction
      - ◆ detrusor hyperreflexia = neurologic disease/injury
        - ♦ Supraspinal lesion
          - stroke
          - dementia
          - traumatic brain injury
          - brain tumour
          - cerebellar ataxia
          - NPH
          - cerebral palsy
          - Parkinson's disease
          - MSA: Shy-Drager syndrome
        - ♦ Suprasacral lesion
          - MS
          - SCI
          - MMC + neurospinal dysraphism
          - cervical myelopathy
          - transverse myelitis
          - tabes dorsalis
          - pernicious anemia
          - poliomyelitis
        - ♦ Peripheral lesions
          - disc disease
          - spinal stenosis
          - pelvic surgery
          - herpesvirus infection
          - DM
          - Guillain-Barré syndrome (GBS)
        - ♦ Diffuse lesions
          - Lyme disease
          - hereditary spastic paraplegia
          - tropical spastic paraparesis
          - HIV
          - acute disseminated encephalomyelitis
          - syringomyelia
          - schistosomal myelopathy



## Chapter 24 Questions - Voiding dysfn categorization.doc

- RSD
- amyloidosis
- adult polyglucosan body disease
- Behcet's disease
- neurofibromatosis
- ◆ detrusor instability = no neurologic defect
  - ◆ BOO
  - ◆ postsurgical
  - ◆ bladder stones/FB
  - ◆ bladder tumour
  - ◆ UTI
  - ◆ inflammation
  - ◆ neurologic
  - ◆ psychologic
  - ◆ idiopathic
- decreased compliance
  - ◆ Neurogenic
    - ◆ myelodysplasia
    - ◆ Shy-Drager syndrome
    - ◆ thoracolumbar SCI
    - ◆ TAH
    - ◆ APR
  - ◆ Increased collagen
    - ◆ Infectious: TB cystitis, recurrent UTI
    - ◆ radiation cystitis
    - ◆ IC
    - ◆ chronic indwelling catheter
    - ◆ BOO
  - ◆ Idiopathic
- decreased bladder capacity
- due to outlet (decreased resistance)
- genuine SUI (competent at rest) = hypermobility
  - ◆ lack of suburethral support
    - ◆ childbirth
    - ◆ trauma
    - ◆ pelvic surgery
    - ◆ hypoestrogenic states
    - ◆ aging
  - ◆ pelvic floor laxity, hypermobility
- ISD (poorly functional BN and proximal urethra at rest)
  - ◆ previous pelvic surgery: slings, urethral diverticulectomy, TAH, APR, VIU, TUIBN
  - ◆ neurologic conditions: MMC, anterior spinal artery syndrome, lumbosacral neurologic conditions, Shy-Drager
  - ◆ **radiation**: damages mucosal seal coaptation of the urethra, + local neurologic damage
  - ◆ aging
  - ◆ hypoestrogenic state
  - ◆ fibrosis
- combination
- combination
- failure to empty
  - due to bladder (decreased contractility magnitude or duration)
    - myogenic
    - neurologic
    - psychogenic
    - idiopathic
  - due to outlet (increased resistance)
    - anatomic
      - ◆ prostatic obstruction
      - ◆ BN contracture
      - ◆ urethral stricture

## Chapter 24 Questions - Voiding dysfn categorization.doc

- ◆ urethral compression
- functional
  - ◆ smooth sphincter dyssynergia
  - ◆ striated sphincter dyssynergia
- combination

### What is meant by the term "urethral instability"?

- episodic decreases in outlet pressure unrelated to increases in bladder or IAP

### Name the different classification systems for voiding dysfunction.

- Bors-Comarr Classification
- Hald-Bradley Classification
- Bradley Classification
- Lapedes Classification
- Urodynamic Classification
- ICS Classification
- Functional Classification (Wein)

### Describe the Bors-Comarr classification of voiding dysfunction.

- Sensory neuron lesion
  - incomplete, balanced
  - complete, balanced
- Motor neuron lesion
  - balanced
  - imbalanced
- Sensory-Motor neuron lesion
  - UMN lesion (injury to suprasacral cord)
    - complete/incomplete, balanced/unbalanced
  - LMN lesion (injury to sacral cord or sacral roots)
    - complete/incomplete, balanced/unbalanced
  - mixed lesion
    - upper somatomotor neuron, lower visceromotor neuron
    - lower somatomotor neuron, upper visceromotor neuron
    - N somatomotor neuron, lower visceromotor neuron

### Which group of patients can be described with the Bors-Comarr classification?

- pts w/ neurologic dysfunction: applies best for SCI pts w/ complete neurologic lesions
- cannot be used at all for pts w/ non-neurologic disease

### What is meant by balanced or unbalanced in the Bors-Comarr classification?

- unbalanced: presence of >20% PVR urine in pt w/ UMN lesion or >10% PVR in pt w/ LMN lesion
- balanced: <20% or 10% residual

### Describe the Hald-Bradley classification of voiding dysfunction.

- supraspinal lesion: synergy b/w smooth and striated sphincter, but defective inhibition of voiding reflex
- suprasacral spinal lesion: UMN lesion
- infrasacral lesion: LMN lesion
- peripheral autonomic neuropathy: DM pt, deficient bladder sensation w/ increasing PVR and muscular decompensation
- muscular lesion: involving detrusor, smooth or striated sphincter

### Describe the Bradley "loop" classification of voiding dysfunction.

- Loop 1: connection b/w cerebral cortex and PMC
  - lesions seen in brain tumour, stroke, cerebral atrophy and dementia
  - involuntary bladder contractions
- Loop 2: intraspinal path b/w sacral spinal cord and PMC
  - lesions seen in SCI → involuntary bladder contraction
- Loop 3: path b/w peripheral detrusor afferents and their paths in the spinal cord (terminate on pudendal motoneurons)
  - causes DSD
- Loop 4
  - Loop 4A: suprasacral innervation of pudendal motor neurons to periurethral striated muscles

## Chapter 24 Questions - Voiding dysfn categorization.doc

- Loop 4B: afferent fibers from periurethral muscles that synapse on pudendal motor neurons in Onuf's nucleus
- allows for voluntary control of striated sphincter
- not useful for non-neurogenic voiding dysfunction

### Describe the Lapedes classification of voiding dysfunction.

- Sensory neurogenic bladder: interruption b/w sensory afferents from bladder to cord/brain
  - due to DM, tabes dorsalis, pernicious anemia
  - results in bladder overdistension, large-capacity bladder w/ decompensation
- Motor neurogenic (motor paralytic) bladder: destruction of parasympathetic motor innervation to bladder
  - due to pelvic surgery, trauma, herpes zoster
  - painful retention, chronic overdistension and decompensation
- Uninhibited neurogenic bladder: injury or disease to suprasacral "corticoregulatory tract"
  - no DSD, low residual urine
  - due to stroke, brain tumour, Parkinson's, demyelinating disease
  - LUTS, UII
- Reflex neurogenic bladder: due to complete interruption of sensory and motor pathways b/w sacral cord and brain stem (UMN)
  - DSD present
  - due to SCI, transverse myelitis, extensive demyelinating disease
  - post-spinal shock: no bladder sensation, inability to voluntarily void
- Autonomous neurogenic bladder: complete motor and sensory separation of bladder from sacral cord (complete LMN lesion)
  - due to damage to sacral roots or pelvic nerves
  - no bladder reflex activity, can develop decreased compliance due to denervation

### Describe the urodynamic classification of voiding dysfunction.

- Detrusor hyperreflexia (or normoflexia): usually due to suprasacral cord injury/disease
  - coordinated sphincters
  - striated sphincter dyssynergia: seen in suprasacral SCI
  - smooth sphincter dyssynergia: seen in autonomic hyperreflexia
  - nonrelaxing smooth sphincter
- Detrusor areflexia: due to bladder muscle decompensation or other conditions that inhibit at level of PMC, sacral cord, bladder ganglia, or bladder smooth muscle → pts often void w/ straining
  - coordinated sphincters
  - nonrelaxing striated sphincter
  - denervated striated sphincter
  - nonrelaxing smooth sphincter

### Describe the ICS (International Continence Society) classification of voiding dysfunction.

- Storage phase
  - Bladder function
    - contractions: normal or overactive (hyperreflexic/unstable)
    - capacity: normal, high, or low
    - compliance: normal, high, or low
    - sensation: normal, increased, reduced, or absent
  - Urethral function
    - normal or incompetent
- Voiding phase
  - Bladder function
    - detrusor activity: normal, underactive, or acontractile
  - Urethral function
    - normal, or obstructive (overactive or mechanical)

### What is meant by "overactive detrusor function"?

- involuntary detrusor contractions during the filling phase of CMG which may be spontaneous or provoked, and which the pt cannot completely suppress

### What is meant by an "underactive detrusor"?

- contraction of inadequate magnitude or duration to empty the bladder w/i a N time span

## **Chapter 24 Questions - Voiding dysfn categorization.doc**

### **What is the Fall and associates' modification of the term "overactive detrusor"?**

- overactive detrusor subdivided into 3 types:
  - uninhibited overactive bladder
    - 1<sup>st</sup> desire to void at normal or subnormal volume, and is followed by an involuntary voiding that the pt can't stop
    - +ve ice-water test
  - phasic detrusor instability
    - urge +/- UUI, N or increased bladder sensation, and spontaneous or provoked phasic bladder contractions >15cm water during filling
    - voiding coordinated, and can usually be delayed
    - -ve ice-water test
  - spinal detrusor hyperreflexia
    - impaired voluntary control of micturition
    - external mechanical stimulation induces detrusor contraction
    - bladder sensation lost or impaired, DSD often occurs
    - +ve ice-water test

### **What is meant by an "overactive bladder"? (OAB)**

- medical condition referring to the sx of freq/urge, +/- UUI
- absence of local pathologic or metabolic factors that would account for these sx

### **What is meant by an "overactive detrusor"?**

- older term: urodynamic finding of involuntary detrusor contractions on CMG





## Chapter 25

### • The Neurourologic Evaluation •

#### What points are important to elicit in the neurourologic pt history?

- Events before sx are noted
  - General hx
    - neurourologic conditions: congenital, metabolic, traumatic, degenerative
    - low back pain, previous spinal cord injury/surgery, Parkinson's, MS, stroke
    - medications: anticholinergic,  $\alpha$ -adrenergics
    - FHx: epilepsy, Huntington's, degenerative conditions
  - GU history
    - voiding habits
    - childhood enuresis
    - UTI, VUR, stones, previous GU surgery
    - obstetric hx
- Current symptoms
  - Urinary sx: onset, duration, time course, aggravating/alleviating factors
    - desire to void, ability to suppress urgency, ability to initiate voiding
    - voiding sx: hesitancy, slow stream, intermittency, straining, PVD, sensation incomplete emptying
    - storage sx: frequency, nocturia, urgency
      - ◆ frequency = void > 8X in 24h
    - incontinence
      - ◆ triggers for UI: running water, positional changes, key in front door
      - ◆ SUI: cough, sneeze, lifting
      - ◆ overflow UI
      - ◆ unconscious UI: w/o any obvious increase in IAP, urge, or conscious recognition that leakage is occurring
      - ◆ continuous UI: constant leakage
  - Associated neurologic sx
    - visual changes
    - sensory changes
    - motor weakness
    - gait abnormalities
  - sexual and bowel dysfunction
    - sensory alterations in genital/perianal area
    - fecal incontinence
    - constipation
    - ED
    - ejaculatory disorders
- Adjuncts to history
  - Pt questionnaire
    - duration and time course of LUTS
    - AUA sx index / IPSS
      - ◆ 7 sx, scored 0-5: mild sx (0-7), moderate (8-19), severe (20-35) + QOL index (0-5)
      - ◆ IPSS does not correlate w/ presence of detrusor instability or BOO
      - ◆ symptomatic pts w/ BOO do not have different scores from pts w/o obstruction that have detrusor dysfunction
    - ICSmale questionnaire
  - Voiding diary: 3-5 days
    - 24h urine output, # voids, voiding interval, diurnal distribution, timing and triggers for UI, functional bladder capacity
    - more reliable than pt's hx → no correlation b/w # voids via history compared w/ voiding diary
  - Pad test → always ask if results are representative of normal function

## Chapter 25 Questions - Neuro GU eval.doc

- wt of all pads/diapers used by pt for 24-48hrs while pt on Pyridium
- **≤8 g over 24 h or ≤2 g over 1 h considered normal**
- short term tests have lower reliability than long-term tests
- ICS: 1hr test w/ series of standard activities
  - ◆ loss of < 1g within error = dry
  - ◆ loss of 1-2g: may be due to weighing error, sweat, or vaginal d/c

### What are the potential causes for incontinence?

- refer to Chapter 26
- urge
  - neurologic disease
  - BOO
  - idiopathic
- stress
  - BN hypermobility
  - ISD
  - MMC
  - sacral SCI
  - urethral trauma
  - pelvic radiation
  - prior UI surgery
- overflow: poor bladder emptying
  - impaired detrusor contractility: medications, nerve injury, myogenic injury (overdistension, age)
  - outflow obstruction: BPH, prostate ca, BN dysfunction, urethral stricture, obstruction from previous UI surgery, cystocele

### What are the causes of unconscious UI?

- unstable bladder contractions, ISD, overflow, extraurethral UI

### What are the important points in the neurourologic physical exam?

- Urologic examination
  - skin: neurofibromas, café au lait spots
  - lower back: evidence of spinal dysraphism (skin dimples, hair tufts, fat deposits)
  - perineal skin integrity
  - pelvic exam
    - degree of vaginal atrophy: loss of rugae, mucosal fragility, petechiae, erosions
    - urethral hypermobility
      - ◆ Q-tip test
        - ◆ lubricated Q-tip placed transurethally into bladder and withdrawn to BN where resistance felt
        - ◆ angle at rest from horizontal, angle w/ straining from horizontal noted
        - ◆ hypermobility = resting or straining angle >30° from horizontal
          - N women may have a +ve test (Fantl 1986)
        - ◆ reproducible but has not been correlated w/ imaging techniques
        - ◆ **no absolute relationship between the degree of urethral motion and the severity of SUI Sx** (Cross 1997)
    - testing for SUI, prolapse: cystocele, rectocele, enterocele, uterus or vaginal cuff
      - ◆ Anterior: Bonney test (fingers), Marshall test (Allis clamp)
        - ◆ may be compressing urethra directly
      - ◆ Middle/apical
        - ◆ enterocele vs. high rectocele: peristalsis in the enterocele
        - ◆ palpation of the rectovaginal septum: combined DRE and vaginal exam
      - ◆ Posterior + perineal body: anterior wall supported w/ speculum, observe defects in rectovaginal septum
    - pelvic floor muscle strength/integrity
  - DRE
    - rectal mass
    - fecal impaction
    - sphincter tone and sensation
    - fascial defect in women w/ rectocele
    - prostate exam
- General neurologic examination

## Chapter 25 Questions - Neuro GU eval.doc

- MSE: general appearance and behaviour, LOC, orientation, memory, speech, comprehension, gait, demeanor, facial asymmetry
- motor examination: strength, atrophy
- sensory examination
- reflexes
  - DTRs
    - ◆ biceps: C5-6
    - ◆ triceps: C7
    - ◆ quadriceps: L3-4
    - ◆ ankle: L5-S2
  - cutaneous reflexes
    - ◆ **abdominal reflex**: lateral to medial scratching of the abdomen causes ipsilateral contraction
      - ◆ afferent/efferents: **segmental** sensory and motor nerves
      - ◆ above umbilicus **T8-T9**
      - ◆ below umbilicus **T10-T11**
      - ◆ may be absent w/ obesity, prior abdo surgery, frequent pregnancy, pyramidal tract involvement above level or peripheral n. lesion
    - ◆ **cremasteric reflex**: stroking inner thigh causes cremasteric contraction
      - ◆ tests **L1-L2**
      - ◆ sensory afferent: ilioinguinal/genitofemoral (L1/2) if the *anterior 1/3 scrotum* is stroked (NB: posterior 2/3 inner has S3 innervation off the posterior scrotal from the perineal n. and the perineal branch of the posterior femoral cutaneous n.)
      - ◆ motor efferent: genitofemoral → cremasteric muscle
  - sacral reflexes
    - ◆ BCR: place finger in rectum, pull Foley or squeeze clitoris/glans → tests integrity of S2-4

### What is the meaning of an absent BCR?

- 30% of neurologically intact females have absent BCR
- incomplete sacral lesions may maintain reflex
- presence or absence of reflex does not establish dx of neurologic lesion

### What lab tests are involved in the neurourologic evaluation?

- Urine
  - urinalysis, urine C&S, cytology
- Renal fn studies
  - urine specific gravity
  - Cr, CrCl

### What radiologic tests are important in the neurourologic evaluation?

- Upper tract
  - US, IVP, renal scan: baseline
  - follow-up study (US) in 6 months
- Lower tract
  - VCUG

### What are the indications for upper tract imaging in pts w/ neurourologic disease?

- high storage/voiding pressures
- DSD
- VUR

### What are the indications for urodynamic evaluation?

(Mnemonic - URODYNAMMIC)

- Unrelenting sx despite tx: pts w/ **persistent LUTS** despite appropriate tx
- **Recurrent incontinence** in women for whom **surgery** is planned
- Outlet obstruction: LUTS suggestive of **BOO** → uroflow study
- Dysraphism: **Children w/ neurospinal dysraphism**
- Young: **men < 50** w/ obstructive LUTS
- Neurologic: pts w/ UI and **neurologic disorders**, obstructive LUTS and **neurologic disease**
- Neurogenic: all neurologically impaired pts w/ **neurogenic bladder** dysfunction
- Associated voiding problems: pts w/ UI and **associated voiding problems**



## Chapter 25 Questions - Neuro GU eval.doc

- Mismatch: pts w/ UI and **mismatch b/w sx** and clinical findings
- Males: **non-neurogenic UI in males**: helpful to r/o significant bladder pathology
- Instability: pts w/ both **obstructive and marked instability** sx
- Confusing: pts w/ UI and **confusing mix of SUI and UUI**
  - Pre-op

### What precautions are important to do before performing UDS?

- pt cooperation
- voiding diary to determine functional capacity pre-test
- should not be performed after recent cysto, w/ UTI, or indwelling
  - convert indwelling to CIC for short time
- antibiotic prophylaxis: SBE prophylaxis, orthopedic/GU prosthesis, multiple instrumentation, increased risk for UTI
- watch for autonomic dysreflexia: sweating, h/a, flushing above level of lesion, htn, reflex bradycardia
  - pre-treatment w/ SL nifedipine 10mg
  - IV hydralazine if does not resolve

### What urodynamic tests are available to evaluate bladder storage function?

- CMG
- bethanechol supersensitivity test
- ice water test
- LPP: DLPP, VLPP
- UPP

### What variables may affect CMG results?

- catheter used and calibration
  - use smallest catheter possible: usually use 8-12F filling cath + separate 3-4F monitoring cath
  - can use fluid manometry, solid state transducer, or fiberoptic techniques
  - eliminate air bubbles in transducer/tubing → causes pressure damping
  - **ideally filling should be performed standing**
  - zero catheter to atmospheric pressure; transducers positioned at the **superior edge of the symphysis pubis**
- filling media
  - material: gas vs. water
  - pH
    - alkali: >8.5 can increase bladder capacity in unstable bladders
    - acid: <3.5 can provoke instability in otherwise stable bladders
  - temperature
- fill rate (ICS definitions)
  - slow fill: <10cc/min
  - medium fill: 10-100cc/min
  - rapid fill: >100cc/min → may cause involuntary contractions
  - children: do 10% of expected capacity per minute → slow (10ml/min), med (20 ml/min), fast (30ml/min)
- provocative maneuvers: try to "unmask" abnormalities of detrusor function
  - fast fill rate ( $\geq 100$  cc/min)
  - Valsalva: cough, sneeze, straining (stress induced instability)
  - change position
    - sitting to standing: 40 cm H<sub>2</sub>O
    - walking: 30 cm H<sub>2</sub>O
    - coughing, sneezing: >50-100 cmH<sub>2</sub>O
    - most pts should have a CMG done in 2 positions
  - running water
  - heel jouncing
  - hand washing in cold water (Petro & Elmsten 1993)
  - ice cystometry
  - bethanechol sensitivity test
- single/multichannel CMG
  - $P_{det} = P_{ves} - P_{abd}$
  - pressure transducers for bladder and rectal catheter must be at same reference level (at upper edge of pubis) and rectal catheter must be zeroed to  $P_{atm}$  at the start of the study

### What are the advantages and disadvantages of gas vs. liquid CMG?

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- Gas
  - Advantages
    - quicker
    - cheap
    - more hygienic if UI
  - Disadvantages
    - unphysiologic (compressible)
    - may provoke instability (forms carbonic acid when dissolved)
    - subtle changes in pressure not detectable (since compressible)
    - rapid fill rates may artifactually  $\Delta$  N bladder response
    - voiding study not possible
    - cannot detect leakage
    - cannot do video studies
    - embolism (air)
- Liquid
  - Advantages
    - more physiologic (not compressible, a fluid)
    - easier to detect leakage
    - can also be used to assess voiding phase
    - may be radiopaque for video studies
    - better control over infusion rates
    - less irritating to the bladder wall
  - Disadvantages
    - cost of agent and equipment
    - components of liquid may provoke instability

### How can one measure Pabd in pts w/o a rectum?

- vagina
- colostomy/ileostomy

### What variables are measured in the CMG?

**\*\*The 8 "C's" of CMG and PFS (Wein)\*\***

| Filling & Storage                  | Emptying             |
|------------------------------------|----------------------|
| Contractions (involuntary bladder) | Contractility        |
| Compliance                         | Complete emptying    |
| Continence (VLPP)                  | Clinical obstruction |
| Cystometric capacity               |                      |
| Conscious sensation                |                      |

- capacity
  - functional bladder capacity
    - largest volume voided as determined by a voiding diary
    - indicates the anticipated volume to which the bladder may be filled during cystometry
  - maximal cystometric capacity
    - volume at which a pt w/ N bladder sensation feels that voiding cannot be delayed
    - usually slightly > functional bladder capacity
    - cannot be determined if no sensation
  - maximal anaesthetic capacity
    - volume of bladder after filling under anaesthesia
- conscious sensation (and volumes at each)
  - first desire to void
  - normal desire to void
  - strong desire to void
  - urgency
    - sensory urgency = stable bladder on CMG w/ sx of urgency and UI
  - pain
- compliance
  - **decreased compliance is < 20 ml/cm H<sub>2</sub>O** → implies a poorly distensible bladder
  - normal pressure is < 10cm H<sub>2</sub>O during the tonus limb, rise of 6-10
  - measured compliance may be dependent on fill rate
- contractions

## Chapter 25 Questions - Neuro GU eval.doc

- number of contractions
  - **any involuntary pressure rise that is associated w/ urgency qualifies as instability**
    - ◆ previously needed pressure rise of  $> 15\text{ cm H}_2\text{O}$  (Nitti 1998)
  - motor urgency = pts w/ urgency and UI w/ cystometrically demonstrated unstable contractions
    - ◆ 40% of pts w/ motor urgency have stable bladder on CMG
- volume at which they occur
- pressure amplitude
- spontaneous vs. triggered by provocation
- if pt able to suppress
- after-contractions: post-micturition contractions → not well understood
  - magnitude usually  $> P_{\text{detQmax}}$

### How can one differentiate b/w a rise in bladder pressure from rapid filling vs. true loss in compliance?

- stop the filling
  - if  $P_{\text{det}}$  remains elevated, then compliance is reduced
  - if  $P_{\text{det}}$  continues to rise, then bladder contraction is occurring

### What are the phases of a typical CMG tracing?

- **Stage I:** Early Filling
  - initial rise in pressure as a response of the muscular and viscoelastic properties of the bladder in response to stretch from filling
  - usu.  $< 10\text{ cm H}_2\text{O}$  w/ slow filling; may have higher peaks w/ rapid filling or infusion of gas
- **Stage II:** Tonus Limb: reflects viscoelastic properties of the bladder wall
  - defines compliance ( $\Delta V/\Delta P$ )
  - neural control likely does not play a role in the tonus limb
  - N = relatively flat curve w/ pressure  $< 10\text{ cmH}_2\text{O}$
- **Stage III:** Capacity
  - bladder wall reaches maximal elongation, increased pressure caused by additional filling
  - limit of elastic and viscoelastic properties
  - any further rise in volume,  $\uparrow\uparrow$  pressure (steep part of the filling curve)
  - practically, discomfort, pain, etc. limit the ability to reach this part of the curve
- **Stage IV:** Initiation of voluntary voiding
  - in bladder pressure w/ associated relaxation of the outlet and bladder emptying (synergic contraction)
  - may not necessarily have voluntary detrusor contraction in testing situation, esp. in supine position
  - inability to void during testing should *not* be called detrusor areflexia but simply, absence of detrusor contraction during CMG
  - not abN unless other clinical or UDS findings are present that substantiate presence of neurologic/myogenic disease

### Describe the bethanechol supersensitivity test.

- after organ deprived of nerve supply, develops hypersensitivity to the normal excitatory NTs for that organ
- CMG performed as baseline → determine average end-fill pressure
- bethanechol  $0.035\text{ mg/kg}$  injected SC
- CMG repeated
  - neurologically intact bladder: pressure increase of  $< 15\text{ cmH}_2\text{O}$
  - denervated bladder: pressure increase  $> 15\text{ cmH}_2\text{O}$
- results unreliable: 76% sensitivity, 50% specificity

### Describe the ice water test.

- mucosal temperature receptors can elicit a spinal reflex contraction to the detrusor
  - normally inhibited by supraspinal centers
  - UMN lesion interrupts these pathways (+ve test), LMN does not (-ve test)
- rapidly inject bladder w/ ice water
  - if ice water expelled by bladder within 1 minute, test +ve
- false -ve: involuntary contraction w/o leakage
- +ve in 97% suprasacral lesions, 91% incomplete suprasacral lesions, 75% pts w/ MS, Parkinson's, stroke

### What factors may cause artefacts in CMG?

- pressure measurement artefacts
  - air bubble or kink in tubing
  - incorrect placement or migration of catheters

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- infusion rate artefacts
  - rapid fill: decreases measured compliance
- pt related issues
  - lack of cooperation
  - outlet incompetence: leak around catheter
  - massive VUR: do videoUDS
- irritating substances
  - catheter
  - fluid medium: temp, pH
  - hypersensitivity states

### What is the difference b/w ALPP and DLPP?

- DLPP = lowest bladder pressure in absence of detrusor contraction at which leakage occurs across the urethra
  - detrusor pressure tends to force the urethral sphincter open
  - reflects resistance of urethra to bladder
  - measure of storage pressure in bladder (compliance)
  - McGuire 1981: myelodysplastic pts w/ DLPP > 40cm H<sub>2</sub>O at increased risk for upper tract deterioration (hydro, VUR)
  - perform during filling phase of CMG
    - leakage of urine noted and Pdet at that instant = DLPP
    - alternatively: remove cath and replace when leakage stops
- ALPP = VLPP = pressure that causes leakage of urine in the absence of a bladder contraction
  - ALPP ≠ DLPP: not identical w/ respect to expulsive force through urethra
    - abdominal pressure will not open a urethral sphincter if the urethra is normally positioned and closed
    - detrusor pressure tends to force urethral sphincter open
  - perform during CMG
    - bladder filled to 150-200cc (1/2 capacity if significant contractions)
    - pt performs slow Valsalva until leakage occurs
    - if no leakage, cough until leakage occurs → tends to be higher due to reflex contraction of pelvic floor
    - if no leakage, fill to 300cc, then capacity and repeat
    - actual pressure to record not clear: Pves vs. Pabd

### What is the clinical utility of VLPP?

- useful when the cause of the UI is not clear: bladder vs. outlet
- VLPP < 60cm H<sub>2</sub>O: presence of significant ISD
- VLPP > 90cm H<sub>2</sub>O: urethral hypermobility w/ minimal ISD
- VLPP 60-90 cm H<sub>2</sub>O: equivocal, suggesting urethral hypermobility and some component of ISD
  - if VLPP > 150cmH<sub>2</sub>O, urethra unlikely to be the cause of pts UI, and the bladder is the culprit

### What factors can cause an inaccurate measurement of VLPP?

- actual pressure used to record VLPP: Pabd, Pves
- volume of bladder at time of measurement
- catheter size: LPP increases if catheter size increases
- vaginal wall prolapse: absorbs increased IAP and lessens force transmitted to BN, may increase VLPP
- pt anxiety: involuntary contraction of pelvic floor
- pt cooperation
- subject position
- detrusor instability: VLPP cannot be interpreted in the presence of UBC's
- guarding reflex: involuntary contraction of striated urethral sphincter: false -ve

### What are the urodynamic risk factors for upper tract deterioration?

- DESD
- low compliance
- BOO
- VUR
- DLPP > 40 cm H<sub>2</sub>O

### What are the different types of UPPs?

- resting/static UPP (RUPP)
  - measures urethral pressures at rest

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- ISD = MUCP < 20cmH<sub>2</sub>O
- records intraluminal pressure along the length of the urethra
- urethral catheter w/ radially drilled side holes slowly withdrawn from the urethra while being perfused w/ liquid
- urethral pressure recorded corresponds to pressure needed to lift the urethral wall off the catheter side holes
- lacks sensitivity and specificity
- stress UPP (SUPP)
  - UPP performed during periods of intermittent stress: cough/Valsalva
  - difficult to perform
- micturitional UPP (MUPP)
  - performed in same manner as standard UPP, but pt voids during catheter withdrawal
  - if urethral obstruction present, UCP distal to obstruction is low while pressures in urethra proximal to obstruction and in pressure are high
  - significant pressure drop during withdrawal corresponds to site of obstruction

### What urodynamic studies are available to evaluate bladder voiding function?

- uroflowmetry
- PVR
- pressure-flow micturition studies
- video UDS
- EMG

### What factors affect result on uroflow?

- detrusor pressure
- urethral patency
- sphincter relaxation
- bladder volume
  - overly distended bladder may cause temporary detrusor decompensation
- bladder contractility
- presence of obstruction
- abdominal straining
- age – in men only
- sex
- voided volume – below 150 and >1000 cc
- position
- catheter size: ≤8Fr recommended
- time of day (circadian variability) – highest in early afternoon
- learning
- emotional stress/environment
  - pregnancy does not change uroflow!

### What different methods for flow rate measurement are available?

- gravimetric method
  - measures weight of collected fluid
- rotating disk method
  - urine flow is directed onto a rotating disk, increasing the inertia of the disk → power needed to keep disk rotating at a constant speed is measured, and is proportional to the flow rate of the fluid
- electronic dipstick method
  - uses capacitance dipstick mounted on the collecting chamber
  - changes capacitance as urine accumulates
  - output signal proportional to the accumulated volume of urine

### What factors affect peak flow rate?

- age and sex
  - in men, Q<sub>max</sub> decreases w/ age
  - in women, Q<sub>max</sub> not affected w/ age
- chance
  - 40% of men have a difference in Q<sub>max</sub> of > 2cc/sec b/w voids, 20% have difference of > 4cc/sec
- voided volume
  - voided volumes < 150cc have inaccurate flow patterns and parameters
  - **Siroky nomogram:** depicts maximal and average flow rates at different bladder volumes for men

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→ Liverpool nomogram: created from voids of >500 men and women

### What are the normal values for Qmax?

- Men
  - <40yrs: >22
  - 40-60yrs: >18
  - >60yrs: >13
- Women
  - <50yrs: >25
  - >50yrs: >18

### How can uroflow help diagnose BOO?

- uroflow alone insufficient to diagnose BOO as it cannot distinguish this from poor contractility
- Qmax < 15cc/sec have better subjective outcome after TURP
- Qmax > 15cc/sec have lower incidence of BOO preoperatively (from PFS)
- further UDS needed in men w/ Qmax > 12-15cc/sec
- ICS-BPH study
  - 70% of men w/ Qmax < 10cc/sec have BOO (Reynard 1998)

### What is meant by high flow obstruction?

- Qmax > 15cc/sec w/ associated Pdet > 100cm H<sub>2</sub>O
  - also benefit from TURP

### What are the ICS definitions of the following terms:

- premicturition pressure = intravesical pressure just before the onset of the voiding contraction
- detrusor opening pressure = Pdet recorded at the onset of measured flow
  - elevated in pts w/ infravesical obstruction
- opening time = time from initial rise in Pdet to onset of flow through urethra
- detrusor pressure at maximal flow = PdetQmax = magnitude of voiding contraction at time when flow rate at its maximum
  - if PdetQmax > 100cm H<sub>2</sub>O, implies BOO even if flow rate normal
- maximal detrusor pressure = maximal pressure recorded regardless of flow
- postvoid residual = volume of urine remaining in bladder immediately after voiding
  - PVR of 0 does not exclude BOO or bladder dysfunction

### What is the utility of PVR?

- like uroflow, PVR is an integrated assessment of the bladder and outlet during emptying
  - measured on US or I+O
- definitions of N – controversial and variable depending on the clinical situation
  - adults: <25ml suggested; **volumes >100 warrants “careful surveillance and/or Tx” (Homma 1999)**
  - as a guideline, 25% of expected bladder capacity also suggested
- considerable intraindividual variation on sequential measurements
  - lower values (<100 ml) tend to be more reproducible than high values
- generalizations
  - consistently and significantly ↑ PVR indicate detrusor failure ± outlet obstruction
  - conversely, ↓ PVR is compatible w/ N function, though may be found w/ detrusor compensation for BOO

### What is the normal Pdet during voiding?

- male = 40-60cm H<sub>2</sub>O
  - pressures > 80 may indicate obstruction
- female = lower pressures

### What are the indications for pressure-flow studies?

- to **differentiate b/w BOO vs. poor contractility** causing low Qmax
- to identify pts w/ high pressure obstruction and normal flow rates: **high flow obstruction**
- if **surgery** being contemplated in men w/ LUTS
- pts w/ LUTS and hx of **neurologic disease**
- **younger men** w/ LUTS
- women post-cystourethropy w/ retention: controversial → not standard

## Chapter 25 Questions - Neuro GU eval.doc

### How does presence of LUTS and flow rate predict presence of obstruction?

- 1/3 of men w/ LUTS do not have UDS evidence of obstruction
- 25-30% of men w/ low flow rates have detrusor hypocontractility
- 7% of men w/  $Q_{max} > 15 \text{ cc/sec}$  are obstructed

### What are the different types of pressure-flow plots available?

- Abrams-Griffiths nomogram
  - $P_{det}Q_{max}$  vs.  $Q_{max}$
  - based on "theoretical analysis and empirical observation"
  - 3 regions dividing obstructed from equivocal from nonobstructed
    - wide equivocal area, separated by 2 lines
    - $y = mx + b$  (slope =  $2 \text{ cmH}_2\text{O}$ ) →  $P_{det}Q_{max} = 2Q_{max} + \text{AG number}$ 
      - ◆ so AG number =  $P_{det}Q_{max} - 2Q_{max}$
  - plot  $P_{det}$  vs. flow at each point in PFS → also  $Q_{max}$  and  $P_{det}Q_{max}$
  - if  $P_{det}Q_{min} > 40 \text{ cmH}_2\text{O}$ , then obstruction is present → if  $< 15 \text{ cmH}_2\text{O}$ , no obstruction
  - degree of obstruction graded by AG number =  $P_{det}Q_{max} - 2Q_{max}$
- Schafer nomogram
  - relates BOO to changes in urethral resistance, independent of detrusor contractility
  - based on consideration of urethra as distensible tube w/ flow controlling zone
  - urethra requires certain amount of pressure to open ( $P_{muo}$ ) → equivalent of  $P_{det}Q_{min}$
  - LinPURR = linear passive urethral resistance relation = flow vs. pressure from opening to  $Q_{max}$
- urethral resistance factor (URA) nomogram
  - from large # of adults w/ and w/o BOO
  - not intended for use in children
- CHES model
- ICS Provisional nomogram
  - very similar to AG nomogram, except boundary b/w unobstructed and equivocal moved to reduce the size of the equivocal region
  - plot  $P_{det}Q_{max} * Q_{max}$  value to determine category of urethral resistance

### What is the bladder outlet obstruction index (BOOI)?

- $BOOI = P_{det}Q_{max} - 2(Q_{max})$ 
  - $BOOI > 40$  = obstruction
  - $BOOI < 20$  = no obstruction
  - $BOOI 20-40$  = equivocal
- same as AG number (estimate of  $P_{det}Q_{min}$ )

### What is the bladder contractility index (BCI)?

- $BCI = P_{det}Q_{max} + 5Q_{max}$ 
  - $BCI > 150$  = strong
  - $BCI < 100$  = weak
  - $BCI 100-150$  = normal contractility

### What are the advantages and disadvantages of ambulatory UDS?

- Advantages
  - can be used in pts in whom conventional UDS are unsuitable or unable to reproduce LUTS that are being investigated
  - more sensitive than conventional CMG in detection of unstable contractions
  - can detect detrusor instability in pts in whom a CMG is nondiagnostic
- Disadvantages
  - pt must play an active role
  - pt compliance may be a source of significant error
  - significance of increased detection of DI is unclear

### What are the differences in pressure readings in AUM vs. conventional UDS?

- filling pressures w/ AUM significantly lower than conventional
- higher voiding pressures and flow rates and lower voided volumes on AUM vs. conventional

### What are the indications for video UDS?

- simultaneous evaluation of structure and function of GU tract needed to make a diagnosis

## Chapter 25 Questions - Neuro GU eval.doc

- Incontinence
  - helps identify presence and degree of BN hypermobility, degree of proximal urethral weakness, and degree and type of cystocele
  - improves accuracy of VLPP
- Post-operative: RP, APR, TAH
- Obstruction + complex BOO: to determine location of an obstruction
  - at BN, prostatic urethra, or distal sphincter
- Reflux
- Neurogenic bladder dysfunction
  - detects leakage or VUR, which artefactually increase bladder compliance
  - diagnoses DSD and presence of tics
- Other things in the bladder: to identify associated diverticulae, fistulae, and stones

| NGB Dysfunction  | Incontinence      | Complex BOO          | Iatrogenic Dz | Miscellaneous    |
|------------------|-------------------|----------------------|---------------|------------------|
| SCI              | ISD               | Urethral             | Post-APR      | Pretransplant    |
| CVA VD           | Hypermobility     | obstruction in       | Post-RRP      | evaluation       |
| Parkinson's      | associated        | females              | incontinence  | Malfunctioning   |
| MS               | incontinence      | BN obstruction       | Post-radical  | AUS              |
| Myelomeningocele | Failed            | Documenting poor     | hysterectomy  | Pediatric VD     |
| Suspected poor   | incontinence      | detrusor             |               | Identify assoc.  |
| bladder          | procedure         | contractility        |               | pathology: tics, |
| compliance       | Urge incontinence | Identifying the site |               | VUR, etc.        |
|                  |                   | of obstruction*      |               |                  |

VD: voiding dysfunction; \* esp. young men w/ voiding function and NGB w/ DSD (?BN, prostatic urethra, distal sphincter)

### What is assessed during video UDS?

|                     |                             |
|---------------------|-----------------------------|
| <b>Upper tracts</b> | VUR                         |
| <b>Bladder</b>      | Capacity                    |
|                     | Shape                       |
|                     | Diverticula, trabeculations |
|                     | Cystocele                   |
| <b>Bladder neck</b> | Position                    |
|                     | Open vs. closed at rest     |
|                     | Opening w/ urge/UBC         |
|                     | Descent w/ straining        |
|                     | Contractures                |
| <b>Urethra</b>      | BPH                         |
|                     | Strictures                  |
|                     | Diverticula                 |
|                     | Sphincter activity          |
| <b>SUI</b>          | Type (functional abN)       |
|                     | Severity (ALPP)             |

### What are the different forms of electrophysiologic testing of the bladder?

- kinesiology studies
  - examine sphincter activity during bladder filling and voiding: sphincter EMGs
- neurophysiologic tests
  - examine the integrity of innervation of the muscle: measures MUAPs
  - nerve conduction studies

### How does one perform sphincter EMG studies?

- surface electrodes placed on skin/mucosa over muscle of interest, or needle electrodes directly into muscle
  - preferable to record from periurethral area
- before bladder filling, pt asked to demonstrate volitional control over sphincter
- BCR tested
  - burst of EMG activity = intact sacral arc
- bladder filled
  - as bladder fills, progressive recruitment of sphincter activity
  - before onset of voiding, sphincter relaxes and remains so for duration
  - abnormal result if sphincter contracting during voiding



## Chapter 25 Questions - Neuro GU eval.doc

- DSD: if neurologic disease present
- pelvic floor hyperactivity / dysfunctional voiding: if no neurologic disease
- sphincter bradykinesia: seen in Parkinson's disease → delay in relaxation of sphincter at onset of voiding due to skeletal muscle hypertonicity

### What are the indications for sphincter EMGs?

- limited role: video UDS provides as much info as usually needed
- in any pt in whom there is a suspicion of discoordination b/w sphincter and bladder
  - SCI
  - neurologic disease: Parkinson's, spina bifida, MS, MSA
  - voiding dysfunction and upper tract changes in kids
  - young women w/ urinary retention

### What are the characteristics of a normal motor unit action potential (MUAP)?

- amplitude: 50-300uV
- duration: 3-5msec
- frequency: 1-4 Hz

### What are the characteristics of an abnormal MUAP?

- polyphasic potentials (>5 deflections)
  - up to 15% MUAPs can be polyphasic and be considered normal
- fibrillation potentials
- +ve sharp waves
- bizarre high frequency forms

### Why do abnormal MUAPs occur?

- **motoneuron damaged, and muscle fibers that have lost their innervation become reinnervated by adjacent healthy nerves**
- MUAP changes from simple waveform to larger more complex → polyphasic potential

### What are the indications for measuring MUAPs?

- evaluation of the pt w/ bladder dysfunction of unknown cause and in whom neuropathy is suspected
- medicolegal cases

### How do nerve conduction studies work?

- performed by stimulation of a peripheral nerve and monitoring time taken for a response to occur
  - **latency** = time from stimulation to response
  - BCR latency most commonly measured
- evoked potentials
  - apply stimulus to nerve and measure cortical response

**Chapter 25 Questions - Neuro GU eval.doc****\*\*Causes of Overactive/Unstable/Involuntary Bladder Contractions\*\***

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| <b>Neurogenic<br/>(Detrusor Hyperreflexia)</b> | <b>Non-Neurogenic/Idiopathic<br/>(Detrusor Instability)</b> |
|--|---|
| <b>Suprasacral Spinal Lesions</b> (PMC-Sacral) | Idiopathic urethral obstruction                             |
| SCI  | UTI/inflammation (prob. most common)                        |
| MS   | BOO: BPH (men), urethral stricture/scar<br>(women)          |
| Spina bifida                                   | Bladder stones  |
| Transverse myelitis                            | Bladder tumor   |
| MMC  | Foreign body  |
| <b>Supraspinal Lesions</b>                     | Sphincteric incontinence                                    |
| CVA  | Ageing  |
| Brain tumor                                    |   |
| Parkinson's disease                            |   |
| Shy-Drager                                     |   |
| Hydrocephalus                                  |   |
| MS   |   |
| CP   |   |
| <b>General</b>                                 |   |
| DM   |   |

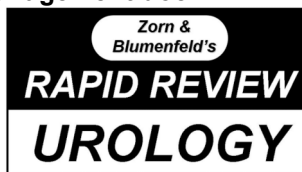
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| <b>Low Compliance</b>   | <b>High Compliance</b>  |
|---|---|
| <b>Pathologic Causes</b>  |   |
| <b>Decreased Accommodation - ↑ Collagen</b>                                 |   |
| 1. infectious: TB, schistosomiasis  | 1. prolonged and gradually progressive delayed voiding  |
| 2. radiation  | 2. sensory impairment; most commonly DM or pernicious anemia (B12), EtOH w/ peripheral neuropathy |
| 3. chronic BOO  | 3. SCI – period of spinal shock lasting 6-8 weeks post injury                                     |
| 4. defunctionalization  |   |
| - prolonged catheterization: muscular hypertonia, mucosal and mural changes |   |
| - defunctionalization   |   |
| 5. idiopathic: interstitial cystitis  |   |
| 6. surgery  |   |
| <b>Increased Tone – Neurogenic</b>  | <b>Artificially (False +ve) Causes of decreased</b>   |
| 1. MM   | 1. filling beyond distensibility limits (stage III of CMG)  |
| 2. Shy-Drager   | 2. rapid filling rate ( <i>exceeds rate of stress relaxation</i> )                                |
| 3. Thoracolumbar SCI  |   |
| 4. surgery: hysterectomy, APR   |   |

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(McGuire 1981, Ghoneim 1989, Steinkohl 1989, Zoubek 1989, McGuire 1994)



## Chapter 26

### • Neuromuscular Dysfunction of the Lower Urinary Tract and its Management •

#### What are the various therapies available to facilitate urine storage/bladder filling?

- Bladder related (inhibiting contractility, decreasing sensory input or increasing capacity)
    - behavioural therapy
      - **BEHAVE**: for both bladder and outlet
        - ◆ can cause significant reduction in # of incontinence episodes or amount of urine lost: 40-80%
      - Bladder retraining
        - ◆ timed voiding: start at longest consistently dry interval, increase by 15-30min/week
        - ◆ watch w/ timing alarm
        - ◆ review pts response to urge
        - ◆ **must always combine medical therapy w/ bladder retraining**
      - Education
        - ◆ what accounts for urine volume, what is normal
      - Habits: lifestyle changes and dietary modification
        - ◆ fluid limitation, avoid irritants
      - Asked/prompted voiding + scheduled toileting
        - ◆ for mentally challenged ppl
      - Voiding diary
      - Exercises: pelvic floor physiotherapy and rehabilitation
        - ◆ Basic: at home
          - ◆ Kegel exercises: quick flicks
          - ◆ Vaginal cones
          - ◆ Simple home perineometry
        - ◆ Advanced: require trained therapist/equipment
          - ◆ office-based EMG biofeedback
            - biofeedback = any technique that trains pts control via providing information about that fn
          - ◆ passive techniques
            - peripheral electrical stimulation (E-stim)
            - magnetic stimulation
  - pharmacologic therapy
    - anticholinergic agents
    - drugs w/ mixed actions
    - CCB
    - K channel openers
    - PG inhibitors
    - $\beta$ -adrenergic agonists
    - $\alpha$ -adrenergic antagonists
    - TCAs, SNRIs
    - DMSO
    - polysynaptic inhibitors
    - capsaicin, resinaferotoxin
  - bladder overdistension
  - electrical stimulation and neuromodulation
  - acupuncture
  - denervation procedures: central (subarachnoid block), less central (sacral rhizotomy), and peripheral (Botox)
  - augmentation cystoplasty
- Outlet related (increasing outlet resistance)
  - Behavioural therapy (as above)
  - vaginal/perineal occlusive and supportive devices, urethral plugs

## Chapter 26 Questions - Voiding dysfn management.doc

- Pharmacologic therapy
  - $\alpha$ -adrenergic agonists
  - TCAs, SNRIs
  - $\beta$ -adrenergic agonists or antagonists
  - estrogens
- E-stim
- injection therapy → nonsurgical urethral compression: collagen, durasphere
- surgical therapy
  - BN suspension
  - sling
  - BN closure
  - AUS
  - BN reconstruction
  - myoplasty
- Circumventing the problem
  - ADH-like agents
  - short-acting diuretics
  - CIC
  - external collecting devices
  - absorbent products
  - indwelling catheter
  - diversion

### What are the various therapies available to facilitate bladder emptying?

- Bladder related (increasing intravesical pressure or facilitating bladder contractions)
  - external compression, Valsalva
  - promotion or initiation of reflex contraction: trigger zones, bladder "training"
  - pharmacologic therapy: parasympathomimetic agents, PGs, blockers of inhibition ( $\alpha$ -adrenergic antagonists, opioid antagonists)
  - surgical therapy
    - reduction cystoplasty: use debatable
    - bladder myoplasty
  - electrical stimulation
    - directly to bladder or cord
    - directly to nerve roots
    - intravesical (transurethral)
    - neuromodulation
- Outlet related (decreasing outlet resistance)
  - at a site of obstruction
    - pharmacologic therapy:  $\alpha$ -adrenergic antagonists, 5  $\alpha$ -reductase antagonists, LHRH agonists/antagonists, antiandrogens
    - prostatectomy
    - TUIBN
    - urethral stricture repair/dilation
    - intraurethral stent
    - balloon dilation of stricture/contracture
  - at level of smooth sphincter
    - pharmacologic therapy:  $\alpha$ -adrenergic antagonists,  $\beta$ -adrenergic agonists
    - TURP, TUIP
    - V-Y plasty
  - at level of striated sphincter
    - behavioural therapy +/- biofeedback
    - psychotherapy
    - pharmacologic therapy: benzodiazepines, baclofen, dantrolene,  $\alpha$ -adrenergic antagonists, BoTox
    - urethral overdilation
    - surgical sphincterotomy
    - urethral stent
    - pudendal nerve interruption
- Circumventing the problem
  - CIC

## Chapter 26 Questions - Voiding dysfn management.doc

- indwelling catheter
- diversion

### What is the general voiding pattern with each of the following lesions:

- lesion above brain stem: IBCs (involuntary bladder contractions) w/ smooth and striated sphincter synergy
  - sensation and voluntary sphincter function generally OK
    - bradykinetic EUS w/ Parkinson's
    - open incompetent smooth sphincter w/ Shy-Drager
  - may be decreased sensation of LUT events w/ stroke or tumour
  - impaired detrusor activity (DHIC) w/ Parkinson's, Shy-Drager, or MS
  - striated sphincter dyssynergia in 25% of pts w/ CP, 30-65% of pts w/ MS
  - areflexia may occur initially or become permanent
- lesion of cord b/w T6-S2: IBCs w/o sensation, smooth sphincter synergy, striated DSD, normal compliance
  - if above T6: smooth DSD, autonomic hyperreflexia
- spinal cord trauma below S2: detrusor areflexia w/ decreased compliance, fixed striated sphincter
  - generally no involuntary contractions
  - competent nonrelaxing/open smooth sphincter: due to sympathetic or parasympathetic decentralization
- interruption of peripheral reflex arc: similar to distal SCI
  - detrusor areflexia, decreased compliance
  - incompetent smooth sphincter, fixed striated sphincter w/ radical pelvic surgery
  - CNR smooth sphincter w/ disc disease

### What disease processes at or above the brain stem cause voiding dysfunction?

- stroke, dementia
- traumatic brain injury
- brain tumour
- cerebellar ataxia
- NPH
- cerebral palsy
- Parkinson's disease
- MSA: Shy-Drager syndrome

### What is the function of the smooth and striated sphincter with the following disorders:

#### Smooth Sphincter

| Synergic   | Dyssynergic                   | Open, incompetent @ rest  | Competent, non-relaxing      |
|--|-------------------------------|---|------------------------------|
| CVA<br>Brain tumor<br>CP<br>Parkinson's<br>MS<br>SCI – suprasacral<br>Tabes, pernicious anemia<br>DM | SCI – autonomic hyperreflexia | Shy-Drager<br>SCI – sacral (may develop)<br>MMC<br>Radical pelvic surgery | SCI – sacral<br>Disc disease |

#### Striated Sphincter

| Synergic   | Dyssynergic  | ± Impaired voluntary control | Fixed tone                                    |
|--|--|------------------------------|---|
| CVA*<br>Brain tumor<br>CP*<br>Parkinson's<br>Shy-Drager<br>MS*<br>Tabes, pernicious anemia<br>Disc disease<br>DM | CP (25%)<br>MS (30-65%)*<br>SCI – suprasacral<br>SCI – autonomic hyperreflexia | CVA*<br>CP*                  | SCI – sacral<br>MMC<br>Radical Pelvic surgery |

## **Chapter 26 Questions - Voiding dysfunction management.doc**

### **What changes in the bladder occur due to BOO?**

- increased contractile protein synthesis
- increase in ratio of type 3 to type 1 collagen
- localization of type 3 collagen changes
- partial denervation due to damage of intrinsic innervation of bladder smooth muscle from pressure and ischaemia
- increased incidence of +ve ice-water test

### **How does voiding dysfunction present after stroke?**

- urinary retention after acute event → detrusor areflexia ("cerebral shock")
  - areflexia may persist after stroke
- detrusor hyperreflexia in long term
  - urgency and frequency: most common at night
  - coordinated sphincter activity, try to inhibit involuntary contraction by voluntary EUS contraction
    - may have impaired striated sphincter control
  - sensation generally intact
  - previously existing voiding dysfunction may be aggravated after stroke
- **left-sided hemiplegics complain more** often of urgency: micturition controlled by R side of brain
  - frontal cortex and anterior cingulate gyrus important to emptying
  - PMC on R side
  - voluntary voiding dependent on connections b/w frontal cortex and septal/preoptic region of hypothalamus

### **What are the possible mechanisms for UI associated w/ stroke?**

- impaired voluntary striated sphincter control
- lack of appreciation of bladder filling

### **What is pseudodyssynergia?**

- EMG sphincter "flare" seen during filling CMG
- etiology
  - attempted inhibition of an involuntary bladder contraction by voluntary contraction of the striated sphincter
  - straining to initiate or augment a bladder contraction or in response to discomfort

### **How does stroke location in the brain affect sphincter control?**

- basal ganglia or thalamus: normal sphincter control
- cerebral cortex or internal capsule: inability to contract striated sphincter
- smooth sphincter function generally unaffected by stroke
  - true DSSD does not occur
- brainstem stroke
  - nocturnal frequency, retention, UI
  - no sx if strictly midbrain stroke

### **What is the treatment for voiding dysfunction after stroke?**

- usually due to failure to store secondary to detrusor hyperreflexia
  - focus on decreasing bladder contractility and increasing bladder capacity
- anticholinergics may make pts confused and UI worse

### **How do pts w/ dementia present w/ voiding dysfunction?**

- generally UI
- difficult to know if simply due to lack of awareness or desirability of voluntary control
- tx difficult due to lack of cooperation

### **How do pts w/ traumatic brain injury present w/ voiding dysfunction?**

- initial period of detrusor areflexia
  - lesion above PMC: involuntary bladder contraction → like stroke
  - brain stem lesion (below/in PMC): DESD

### **How do pts w/ brain tumours present w/ voiding dysfunction?**

- depends on location of tumour: usually superior aspect of frontal lobe
  - detrusor hyperreflexia and UI
  - diminished awareness of all lower urinary tract events
    - unable to even attempt suppression of voiding

## Chapter 26 Questions - Voiding dysfn management.doc

- synergic smooth and striated sphincters
- pseudodyssynergia during UDS
- retention in pts w/ lesions in frontal cortex
- posterior fossa: retention or difficulty voiding, UI rare

### How do pts w/ cerebellar ataxia present w/ voiding dysfunction?

- pathologic degeneration of cerebellum +/- brain stem, cord, and dorsal nerve roots → poor coordination, depressed DTRs, dysarthria, dysmetria, and choreiform movements
  - UI and hyperreflexia
  - sphincter synergy
  - retention or high PVR → usually due to areflexia
    - may be associated w/ DSSD, presumably due to cord involvement

### How do people w/ NPH present w/ voiding dysfunction?

- progressive dementia and ataxia in pts w/ normal spinal fluid pressure and distended ventricles
  - UI from detrusor hyperreflexia w/ sphincter synergy

### How do people w/ CP present w/ voiding dysfunction?

- delayed gross motor development, abnormal motor performance, altered tone, abnormal posture, exaggerated reflexes
- most have normal filling/storage and normal emptying w/ normal urinary control
- if adult w/ CP presents w/ acute/subacute change in voiding, usually not related to CP
- most voiding dysfunction: UI, frequency, urgency → detrusor hyperreflexia and coordinated sphincters (DSD in 25%)
- UI can be improved in most pts, difficult if ++ retardation
  - check upper tracts w/ US, Cr, PVR

### What is Parkinson's disease?

- neurodegenerative d/o that affects dopaminergic neurons of substantia nigra, 0.3% of pplx
  - substantia nigra pars compacta: origin of dopaminergic nigrostriatal tract to caudate nucleus and putamen
- DA deficiency in nigrostriatal pathway causes most of the motor sx
  - TRAP: tremor, rigidity, akinesia, Parkinsonian gait
- **asymmetrical, resting tremor, responds to L-dopamine**

### What are the causes of parkinsonism other than PD?

- MSA and Shy-Drager
- progressive supranuclear palsy (PSP)
- cortical-basal ganglionic degeneration
- vascular parkinsonism
- Lewy body dementia

### What is a Lewy body?

- intracytoplasmic eosinophilic hyaline inclusion consistently observed in selectively vulnerable neuronal populations

### How do people w/ PD present w/ voiding dysfunction?

- occurs in 35-70% of pts w/ PD
  - usually storage failure due to bladder overactivity
    - urge, frequency, nocturia, UUI
    - detrusor hyperreflexia on UDS
  - smooth sphincter synergy
  - **pseudodyssynergia** due to **striated sphincter bradykinesia** at onset of voluntary voiding
  - possible detrusor hypocontractility: areflexia uncommon
- do poorly after TURP, due to poor voluntary striated sphincter control
  - poorly sustained bladder contractions w/ slow sphincter relaxation
  - TURP may cause no change or worsening of voiding sx
  - **USD mandatory before any but the simplest and most reversible therapy**

### How does Parkinson's disease differ from Shy-Drager syndrome/MSA?

|            | PD  | SD/MSA  |
|------------|---|---|
| General Sx | - not found in MSA <ol style="list-style-type: none"><li>1. asymmetry of Sx</li><li>2. resting tremor</li></ol> | - parkinsonian dysfunction <i>plus</i> autonomic dysfunction <ol style="list-style-type: none"><li>1. orthostatic hypotension</li></ol> |



## Chapter 26 Questions - Voiding dysfn management.doc

|                          |  |  |
|--------------------------|--|--|
|                          | 3. good response to levodopa   | 2. anhidrosis  |
|                          | - dx of PD usually precedes LUTS and ED by years                                 | 3. cerebellar dysfunction  |
|                          |  | - symptoms of LUTS/ED usu. precedes dx of SD by years  |
|                          |  | - <b>(Sx before Dx in SD)</b>  |
| <b>LUTS</b>              | - nocturia, frequency and urgency w/o UI is common                               | - frequency and urgency w/o UI uncommon  |
|                          | - storage Sx > voiding Sx  | - storage Sx > voiding Sx  |
|                          | - <b>incontinence uncommon</b>   | - <b>incontinence common (75%)</b>   |
| <b>ED</b>                | - 30%  | - >90%   |
| <b>Bladder</b>           | - DH w/ N compliance   | - DH w/ ↓ compliance (due to neuronal involvement)   |
|                          | - ↑ PVR 15%  | - ↑ PVR 50%  |
| <b>Sphincter</b>         | - SMS: closed and synergic   | - <b>SMS: open</b>   |
|                          | - STS: pseudodyssynergia and/or bradykinesia                                     | - STS: denervated, weak → seen on EMG  |
| <b>Management issues</b> | - post-prostatectomy incontinence: <i>likely</i> at ↑ risk; ?mechanism           | - post-prostatectomy incontinence: <i>definite</i> high-risk (>75%); d/t sphincter “denervation” |
|                          | - failure of prostatectomy to improve Sx b/c of weak bladder or STS bradykinesia |  |

### What is MSA/SD?

- encompasses several neurodegenerative syndromes
- neurologic lesions in MSA consist of cell loss and gliosis in widespread areas, **more so than in PD**  
→ neurodegenerative syndrome, characterized by extrapyramidal, cerebellar, pyramidal, and autonomic involvement
- more severe sx in MSA, erection usually affected
- generally progressive w/ poor prognosis

### What are the clinical characteristics of Shy-Drager?

- orthostatic hypotension
- anhidrosis
- varying degrees of cerebellar and parkinsonian dysfunction

### How do people w/ MSA present w/ voiding dysfunction?

- initial sx of UI, freq/urge (less commonly)
  - hyperreflexia
  - decreased compliance (due to peripheral autonomic neuronal degeneration)
  - difficulty in initiating and maintaining voiding: usually from pontine and sacral cord lesions
  - open BN (ISD) → seen only in Shy-Drager, not in PD
  - urinary sx precede or present w/ sx of parkinsonism
- compared w/ PD, who present w/ freq/urge, **no UI**
  - sx present after dx of PD
- treatment difficult, usually doesn't work
  - TURP hazardous → UI
  - facilitate storage → CIC often desirable, but not candidates if advanced disease

### What diseases primarily involving the spinal cord can cause voiding dysfunction?

- MS
- SCI
- MMC + neurospinal dysraphism
- cervical myelopathy
- transverse myelitis
- tabes dorsalis
- pernicious anemia
- poliomyelitis

### What is the cause of MS?

- autoimmune-induced focal neural demyelination in brain and cord, characterized by axonal sparing  
→ demyelination causes impaired conduction in axonal pathways

## Chapter 26 Questions - Voiding dysfn management.doc

- 2X increase in women
- lesions (called plaques) range from 1-40mm, scattered throughout white matter
- demyelinating process involves lateral corticospinal and reticulospinal columns of cervical cord
  - 100% cervical cord involvement
  - 40% lumbar cord, 20% sacral cord
  - cerebral cortex and midbrain: may cause euphoria and intellectual deterioration

### How do pts w/ MS present w/ voiding dysfunction?

- usually storage failure due to detrusor hyperreflexia +/- DESD
- 50-90% complain of voiding sx at some time
  - acute retention or acute onset of urge/freq due to hyperreflexia → **always think of MS in the woman w/ AUR**
  - **LUTS may be the presenting sx in up to 10%** → usually retention or acute onset of urge/frequency
- detrusor hyperreflexia most common finding on UDS
  - of pts w/ hyperreflexia, 30-65% have DESD, 60% have impaired contractility
  - areflexia may also occur
  - smooth sphincter synergy, striated sphincter variable (normal, DSD, flaccid)
- 3 basic patterns of UDS:
  - DH + synergic sphincters: 40%
  - DH + DESD: 30%
  - detrusor areflexia: 25%
- normal bladder sensation

### What are the most important factors that predispose MS pts to GU complications?

- DESD in men
- high Pdet during filling (>40 cm H<sub>2</sub>O)
- indwelling catheter

### What is the treatment of voiding dysfunction from MS?

- aggressive and anticipatory medical management
  - anticholinergics +/- CIC
  - behavioural therapy

### What are the causes of SCI?

- violence
- fracture
- vascular injury
- infection
- disc prolapse
- severe hyperextension

### Describe the phenomenon of spinal shock and its GU manifestations.

- after SCI, period of decreased excitability occurs at and below level of lesion
- absent somatic reflex activity and flaccid muscle paralysis x days-months, but may return in minutes-hrs
  - BCR usually 1<sup>st</sup> to return
- bladder is acontractile and areflexic
- BN closed and competent → UI not present
- guarding reflex absent, no voluntary control
- urinary retention
- eventually return of detrusor contractility
  - reflex activity poorly sustained at first
  - involuntary voiding between catheterizations, occurs along w/ recovery of lower extremity DTRs

### What are the characteristics of the following SCI syndromes?

|                      |   |
|----------------------|---|
| <b>Central cord</b>  | - corticospinal and spinothalamic tracts organized such that sacral fibers are more lateral and cervical fibres more medial → caudal fibres protected |
|                      | - “upside-down” quadriplegia: weakness arms > legs  |
|                      | - usu. hyperextension injuries  |
| <b>Brown-Sequard</b> | - injury more prominent on one side than the other  |
|                      | - ipsilateral: motor and fine touch and proprioception loss   |

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|                                      |  |
|--------------------------------------|--|
|                                      | - contralateral: pain and temperature loss   |
|                                      | - usu. penetrating injuries and asymmetric herniations                               |
|                                      | - pure B-S syndrome rare`  |
| <b>Anterior cord</b>                 | - usu. anterior spinal artery injury from flexion injuries, acute central herniation |
|                                      | - weakness and loss of pain and temperature below the level of the lesion            |
|                                      | - rare in pure form  |
| <b>Cauda Equina-Conus Medullaris</b> | - primarily spinal nerve roots $\pm$ conus   |
|                                      | - flaccid (rather than spastic) motor weakness                                       |
|                                      | - all sensory modalities lost  |
|                                      | - sacral reflexes partial or completely lost   |

### How does SCI location affect bladder function?

- general correlation, but is neither absolute nor specific
- adults: sacral spinal cord starts at T12-L1, cord ends at cauda equina at L2
  - infant: ends at S4
- suprasacral SCI
  - detrusor hyperreflexia, smooth sphincter synergia (w/ lesions below sympathetic outflow) and striated sphincter dyssynergia
  - spasticity of muscles distal to lesion, hyperreflexic DTRs, and abnormal plantar responses
  - DSSD causes functional obstruction w/ poor emptying and high Pdet
  - filling/storage and emptying failure
    - if bladder pressures low (or can be made low w/ medication/OR), tx as emptying failure → continue CIC
    - if high, can perform external sphincterotomy or stent, tx as storage failure → timed stimulation or external collecting device
- sacral SCI
  - detrusor areflexia w/ high or normal compliance
    - may eventually get decreased compliance (response to neural decentralization)
  - CNR smooth sphincter and a fixed striated sphincter not under voluntary control
  - potential RF same as suprasacral: ++ risk of increased Pdet, VUR, hydronephrosis
  - tx to maintain low pressure storage, tx as emptying failure → CIC

### What are the potential GU complications of suprasacral SCI?

- renal failure
- bladder overdistension
- high-pressure storage
- high DLPP
- VUR
- stones
- infection

### What is autonomic dysreflexia (autonomic hyperreflexia)?

- acute massive disordered autonomic (mostly sympathetic) response to specific stimuli in pts w/ SCI above T6-8 (sympathetic outflow)
  - more common in cervical lesions
  - stimulation of afferent impulses that ascend through cord and elicit reflex motor outflow
  - normally, reflexes inhibited by secondary sympathetic inhibitory impulses originating in medulla, but does not occur below level of lesion
  - AH due to unopposed reflex sympathetic outflow from T6-L2
- sx: **headache, htn, flushing** above level of lesion, sweating, bradycardia, arrhythmia
  - Clinical findings: generalized
    - cardiovascular
      - ◆ ↑ SBP – this is the most concerning feature – may be life threatening (up to 300/220 mmHg)
      - ◆ ↑ DBP
      - ◆ bradycardia (usu.  $\approx$ 60 bpm): baroreceptor reflex (aortic arch and carotid body CN X and IX)
      - ◆ arrhythmias: afib, PVC, AV conduction abN
        - ◆ note: SBP normally 90-110 in SCI, therefore ↑ 20-40 mmHg above baseline may indicate AD
    - piloerection
    - skin pallor below the level of the lesion
    - visual sx: scintillations, blurry vision

## Chapter 26 Questions - Voiding dysfn management.doc

- apprehension/anxiety
- Clinical findings: mainly *above* the level of the lesion
- pounding headache (severity has no relationship to the degree of ↑ BP)
  - ◆ pathophysiology: 2° to PGE2 → vasodilation + impairment of autoregulation (digital occlusion of carotids)  
↓ H/A)
- flushed skin
- sweating
- nasal congestion

### What are the requirements for autonomic dysreflexia?

- lesion ≥ T6: above the major sympathetic splanchnic outflow (T6-L2)
  - incomplete or complete injury sufficient
  - may rarely occur to T8 (Bors 1956, Moeller JAMA 1973)
- intact distal [sacral] cord: no AD w/ infarcted sacrum since no reflexes present
- intact spinal reflex: post-spinal shock
- trigger
  - **Urinary: #1 bladder distension**, UTI, stones, DESD, instrumentation, etc.
  - **GI : #2 constipation**, obstruction/ileus, gallstones, PUD/gastritis, hemorrhoids, instrumentation, any intra-abdominal pathology
  - **Genital**: menstruation, pregnancy, STD – vaginitis, coitus/ejaculation
  - **Soft Tissue**: pressure ulcers, ingrown toenail, burns/blisters, tight clothing
  - **Hematologic**: DVT
  - **Surgery**: electrocoagulation

### What are the complications of autonomic dysreflexia?

- intracranial hemorrhage: cerebral and subarachnoid
- seizures
- retinal hemorrhage
- HTN encephalopathy
- CHF (LVF)
- death

### What is the management of autonomic dysreflexia?

| Prevention                                    | General                  | Medical                        | Surgical                      |
|---|--------------------------|--------------------------------|-------------------------------|
| 1) identify Pts at risk (i.e. CMG)            | 1) stop procedure        | 1) antihypertensive medication | - ablative procedures         |
| 2) skin care                                  | 2) ↑ head of bed         | a) CCB 1 <sup>st</sup> choice  | 1) sympathectomy              |
| 3) bowel and bladder regimens                 | 3) loosen tight clothing | 2) spinal anesthesia           | 2) sacral rhizotomy           |
| 4) appropriate anesthetic prior to procedures | 4) Tx inciting cause     |                                | 3) cordectomy                 |
| 5) medical pre-treatment                      | a) urinary retention     |                                | 4) dorsal root ganglionectomy |
|   | b) fecal impaction       |                                |                               |
|   | c) other                 |                                |                               |

### Prevention of procedure-related AD

- most common at induction: occurs in 30%
- choice of anesthetic: anesthesia ↓ incidence, however, NO difference based on type of anesthesia used for induction
  - during the procedure, ↑ in BP occurs in 50-70%, irrespective of type of anesthetic or type of procedure, however, **spinal or carefully monitored general preferred**
  - in non-anesthetized patients, BP ↑ in 90%
  - local anesthetics do not block muscle proprioception and therefore if bladder distention is the triggering factor, a **spinal anesthetic** may provide more benefit
- Medications
  - prophylactic nifedipine sl 10 mg 30 min before OR (Dykstra 1987)
  - alpha blockade: Hytrin 5mg
- ESWL w/o spinal or GA but w/ careful monitoring reported (Spirnak JU 1988)

### Management of the acute episode

|                |  |
|----------------|--|
| <b>General</b> | - <b>monitor: BP/HR</b> q2-5 min; then closely x 2 h after BP normalized |
|                | - watch for ↓ BP once stimulus relieved or antihypertensive started      |
|                | - <b>position: ↑ HOB, loosen tight clothing</b>                          |

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### Medical

- do not leave Pt in upright position after an antihypertensive has been given and the episode has passed → will be ++ hypotensive 2° to peripheral venous pooling and ↓ vascular tone
- **survey for urinary retention, constipation or other causes**
  - drain the bladder: catheterize w/ Urojet, irrigate w/ low volumes of *warm* solution
  - disimpact if constipated; use lidocaine instillation first; AXR prn
- Tx only after treating reversible causes
- choice of antihypertensive medication somewhat arbitrary – see lists below
- beware: **many of these Pts are on Viagra** (need 24 h washout period)

### Trop & Bennett. JU 1991

1. prophylaxis or acute episodes: nifedipine sl
2. refractory acute AD: iv hydralazine or trimethaphan
3. frequent recurrent AD: phenoxybenzamine 10 mg tid titrated up to 20 mg prn

### Recommendations of the American Paraplegia Society J Spinal Cord Medicine 1995

- 1) acute management and prophylaxis
  - a) **CCB first choice**: nifedipine: completely safe in AD; 1st choice for Tx and prophylaxis
    - i) use the rapid acting type PO (not SL)
    - ii) NO reported cases of adverse effect in this population (re: serious hypotensive episodes) in the literature through 1996
    - iii) watch for reflex tachycardia → has been reported to cause cardiac events, esp. in elderly
  - b) alpha blockers:
    - i) α-1 antagonists: prazosin 4-8 mg or terazosin 5-10 mg
    - ii) α-2 agonists: clonidine
  - c) other: hydralazine, mecamylamine, phenoxybenzamine
- 2) refractory acute AD: iv vasodilator, e.g. nitroprusside
- 3) frequent recurrent AD: terazosin highly effective (Chancellor 1994, Vaidyanathan 1998)

### Management of chronic, recurrent AD

- medical management as above
- neurologic ablative procedures: interrupt the spinal reflex arc
  1. sympathectomy
  2. sacral rhizotomy
  3. cordectomy
  4. dorsal root ganglionectomy
- irreversible, interfere w/ reflexogenic erections, reflex colonic activity and anal sphincter tone
- may not eliminate AD if the reflex arc is based above the level of the injury (i.e. removing would worsen the spinal level)
- reserved for life-threatening AD

### Management of AD during pregnancy

- preeclampsia: HTN, proteinuria, edema ± HELLP; 3rd trimester; never before 20-24 weeks
- some recommend cystogram in controlled circumstances prior to pregnancy to determine if Pt is at risk for AD
- most common time to develop AD and preeclampsia is in **3rd trimester – AD most likely at delivery – seen in 2/3 of women w/ SCI >T6** (McGregor Amer J Obst Gynec 1985)
  - fetal HR ↑ during episodes of maternal AD
- options
  - **epidural anesthesia Tx of choice** (Trop JU 1991)
  - medical management has been used incl. CCB and hydralazine w/o compromising uterine perfusion

### What are the RF for developing VUR in SCI pts?

- elevated Pves during filling and emptying
- infection

### How does one treat VUR in the setting of SCI?

- normalize lower GU tract urodynamics
  - pharmacotherapy: anticholinergics
  - urethral dilation
  - neuromodulation
  - deafferentation

## **Chapter 26 Questions - Voiding dysfunction management.doc**

- augment
- sphincterotomy
- difficult to correct if thick walled bladder

### **What are the causes of cervical myelopathy?**

- spondylosis
- ossification of the posterior longitudinal ligament
- cervical disk herniation
  - present w/ LUTS, UI, DESD

### **How do pts w/ transverse myelitis present w/ voiding dysfunction?**

- rapidly developing condition w/ paraparesis and sensory disturbances
- usually stabilizes within 2 weeks, not progressive, recovery w/ some neurologic deficits
- similar to SCI

### **How do pts w/ myelodysplasia present w/ voiding dysfunction?**

- areflexic bladder w/ open BN
- bladder fills until resting residual fixed external sphincter pressure reached → leakage occurs
  - DSSD in 10-15%
- improvement in continence after puberty
- neurologic exam fails to predict urodynamic behaviour
- tethered cord: no typical dysfunction

### **How do pts w/ tabes dorsalis present w/ voiding dysfunction?**

- syphilitic myelopathy
  - loss of bladder sensation and large PVR: similar to pernicious anemia
  - "sensory neurogenic bladder"

### **How do pts w/ polio present w/ voiding dysfunction?**

- "motor neurogenic bladder"
- retention, detrusor areflexia, intact sensation

### **What diffuse CNS diseases can cause voiding dysfunction?**

- Lyme disease
- hereditary spastic paraplegia
- tropical spastic paraparesis
- HIV
- acute disseminated encephalomyelitis
- syringomyelia
- schistosomal myelopathy
- RSD
- amyloidosis
- adult polyglucosan body disease
- Behcet's disease
- neurofibromatosis

### **How do the following diseases present w/ voiding dysfunction:**

- Lyme disease: due to spirochete
  - 3 syndromes: encephalopathy, polyneuropathy, leucoencephalopathy
  - variable sx: hyperreflexia, areflexia, retention
- hereditary spastic paraplegia
  - genetically transmitted AD syndrome of central demyelination w/ axon loss and progressive lower extremity spasticity + muscle weakness
  - variable sx: hyperreflexia, DSSD, LUTS, UI, normal detrusor, hyporeflexia
- tropical spastic paraparesis
  - spinal cord myelopathy due to HTLV-1: lower limb weakness and back pain
  - variable sx: areflexia, hyperreflexia, DSSD: depends on if damage to descending tracts, sacral nuclei, or sacral outflow
- HIV
  - variable sx: hyperreflexia, areflexia, hypocontractility: neurogenic voiding = poor prognosis

## Chapter 26 Questions - Voiding dysfn management.doc

- acute disseminated encephalomyelitis (ADEM)
  - acute inflammatory demyelinating disorder of CNS of unknown etiology
    - multifocal lesions, can include entire nervous system
  - variable sx: retention, LUTS, UI
- syringomyelia
  - chronic disorder of spinal cord characterized by dissociated sensory loss and brachial amyotrophy
  - variable sx: due to supranuclear and nuclear types of peripheral autonomic and somatic nerve dysfunction
- schistosomal myelopathy
  - BN obstruction and impaired muscle contractility due to infiltration of smooth muscle
  - UI, hyperreflexia, DSSD
- RSD
  - severe pain and autonomic changes following traumatic injury: etiology unclear

### What diseases distal to the spinal cord can cause voiding dysfunction?

- disc disease
- spinal stenosis
- pelvic surgery
- herpesvirus infection
- DM
- Guillain-Barré syndrome (GBS)

### What direction do discs normally prolapse?

- usually in posterolateral direction → doesn't affect majority of cauda equina
- central prolapse in 1-15% → compression of cauda equina
  - usually compress spinal roots in L4-5 or L5-S1 interspaces

### How do pts w/ prolapsed discs present?

- LBP, sciatica
  - typically associated w/ low back pain radiating to the involved spinal root areas → reflex and sensory loss
    - S1-S2 dermatomes: lateral foot
    - S2-S4 dermatomes: perineum or perianal areas
- saddle sensory loss in perineum, reflex loss
- lower extremity weakness
- bowel dysfunction
- GU sx
  - difficulty voiding w/ straining
  - retention
  - normally compliant areflexic bladder associated w/ normal innervation or findings of incomplete denervation of the perineal floor
  - sexual dysfunction
  - UDS
    - #1 detrusor areflexia w/ N compliance; rarely DH
      - ◆ etiology of DH: unclear – (1) less effect on parasympathetic fibres, (2) sensory > motor impairment
    - STS normally innervated or denervated

### What is the management of voiding dysfunction due to prolapsed disc?

- prelaminaectomy UDS
  - difficult to separate voiding dysfunction from disc from changes due to surgery

### How do pts w/ spinal stenosis present w/ voiding dysfunction?

- due to narrowing of the spinal canal, nerve root canals, or intervertebral foramina
- back pain, lower extremity pain → no consistent pattern: need UDS
- relieved by rest, worsened w/ exercise

### How do pts w/ pelvic surgery present w/ voiding dysfunction?

- similar to sacral cord lesions
  - impaired bladder contractility
  - obstruction due to **residual fixed striated sphincter tone**
  - smooth sphincter open and nonfunctional
  - UI that occurs w/ increased IAP

## Chapter 26 Questions - Voiding dysfn management.doc

- UDS: decreased compliance, poor proximal urethral closure, loss of voluntary control of sphincter  
→ storage and emptying failures
- may present w/ variable degrees of urinary retention
- treat pts w/ CIC, get UDS and wait 6-12 months for return of detrusor function  
→ goal is low-pressure storage w/ periodic emptying

### What is the etiology of voiding dysfunction in pts w/ pelvic surgery?

- denervation or neurologic decentralization  
→ may cause conversion of usual sympathetic  $\beta$  relaxant response to  $\alpha$  contractile effect
- tethering of nerves or encasement in scar
- direct bladder/urethral trauma
- bladder devascularization  
→ **permanent in 15-20%**

### How do pts w/ herpesvirus infections present w/ voiding dysfunction?

- Herpes Zoster virus (HZV)  
→ due to invasion of sacral DRG and posterior nerve roots  
→ retention and detrusor areflexia days to weeks after primary viral manifestations
  - painful cutaneous eruptions
  - fever, malaise
  - perineal and thigh paraesthesias
  - obstipation
  - UI due to detrusor hyperreflexia
- cysto: vesicles in bladder
- most pts recover, but may take months
- Herpes simplex virus (HSV)  
→ sphincter spasm from pain  
→ Eisberg syndrome

### What is the Eisberg syndrome?

- bilateral involvement of the sacral nerve roots w/ HSV
- rapid onset accompanied by sphincteric incontinence w/ CSF pleocytosis

### How do pts w/ DM present w/ voiding dysfunction?

- peripheral and autonomic neuropathy
- first affects sensory afferent pathways, causing insidious onset of impaired bladder sensation
- gradual increase in time b/w voiding w/ delayed emptying
- detrusor overdistension and decompensation
- UDS: decreased sensation, increased capacity, decreased contractility, N compliance, decreased Qmax, increased PVR  
→ usually no DSSD
- tx: control glucose levels, timed voiding, CIC,

### What is the pathophysiology of voiding dysfunction in DM?

- increased in blood sugar increases intracellular accumulation of glucose and its metabolic products
- hyperglycemia leads to microvascular and neurologic complications
- loss of myelinated and demyelinated fibers, wallerian degeneration, and blunted nerve fiber reproduction and function
- increased accumulation of polyols (sorbitol) through the aldolase reductase pathway
- formation of advanced glycosylation end products

### How does Guillain-Barré syndrome present w/ voiding dysfunction?

- inflammatory demyelinating disorder of the peripheral nervous system  
→ may be life threatening  
→ rapidly evolving symmetrical limb weakness, loss of DTRs, absent or mild sensory signs, variable autonomic dysfunctions
- due to aberrant immune responses against peripheral nerve components  
→ triggered by a preceding bacterial or viral infection  
→ immune responses directed towards infecting organisms cross reacting w/ neural tissues  
→ autonomic neuropathy common
- cardiac arrhythmia, htn, hypotension, bowel/bladder/sexual dysfunction
- variable voiding dysfn: AUR, LUTS, UII, SUI



## Chapter 26 Questions - Voiding dysfn management.doc

- tx w/ reversible tx (CIC, anticholinergics) while waiting for resolution

### How can one classify the different types of DESD?

- type I: concomitant increase in both detrusor pressure and EMG activity  
→ at peak of detrusor contraction, sphincter suddenly relaxes, and unobstructed voiding occurs
- type II: sporadic contractions of the striated sphincter throughout the detrusor contraction
- type III: crescendo-decrescendo pattern of sphincter contraction that results in BOO throughout the entire detrusor contraction

### What are the complications of DESD?

- VUR
- upper tract deterioration
- stones
- sepsis
- UVJ obstruction

### What are the potential treatment options for DESD?

- CIC + anticholinergics
- sphincterotomy
- stent placement
- botox
- indwelling
- urinary diversion

### What is the Hinman syndrome?

- involuntary obstruction at the striated sphincter in the absence of demonstrable neurologic disease

### How do pts w/ bladder neck dysfunction present w/ voiding dysfunction?

- due to incomplete opening of BN during voluntary or involuntary voiding
- almost exclusively in young and middle-aged men  
→ young, anxious, high-strung individuals
- complain of long-standing storage and voiding sx
- obstruction localized at level of BN on video UDS or UPP
- etiology unknown  
→ ?abnormal arrangement of BN musculature
- treatment  
→ partial relief w/  $\alpha$ -blockers  
→ definitive tx w/ TUIBN

### What is meant by a *trapped prostate*?

- BPH in the setting of BN dysfunction

### What is the Fowler syndrome?

- urinary retention in young women in the absence of overt neurologic disease
- women aged 20-30, unable to void over past 12hrs
- sphincter EMG demonstrates unique EMG abnormality  
→ complex repetitive discharges and decelerating bursts → impairs sphincter relaxation

### What are the contributing factors to postoperative urinary retention?

- traumatic instrumentation
- bladder overdistension
- diminished awareness of bladder sensation
- decreased bladder contractility
- increased outlet resistance
- decreased voiding reflex
- nociceptive inhibitory reflex
- preexistent outlet pathology

### What is the DDx for urinary retention?

- Male

## Chapter 26 Questions - Voiding dysfn management.doc

- Bladder
  - Infection: cystitis
  - Neurologic
    - ◆ Causes of areflexia
      - ♦ MS
      - ♦ SB occulta
      - ♦ tethered cord
      - ♦ sacromyeloradiculitis: herpesvirus (zoster and simplex), CMV, EBV, HIV; Lyme disease
      - ♦ cauda equina/lumbar disc prolapse
      - ♦ anovesical inhibitory reflex (e.g. postop anal surgery)
  - Pharmacologic
    - ◆ anticholinergic: antipsychotics, bladder relaxants
    - ◆ TCA/SSRI: imipramine
    - ◆ opioids: ↓ sensation → bladder overdistention (+ direct action on CNS opioid receptors? – check this)
    - ◆ CCB
    - ◆ baclofen
    - ◆ β-blockers
    - ◆ α-agonists
    - ◆ K channel openers
    - ◆ PG inhibitors
- Outlet
  - Mechanical BOO
    - ◆ intrinsic
      - ♦ prostate: BPH, Ca prostate, prostate infarction, mechanical BOO (?edema etc.), neurogenic (failure of sphincter relaxation)
      - ♦ urethra: stricture, urethral Ca
      - ♦ bladder neck contracture
      - ♦ intraluminal: clot, stone
    - ◆ extrinsic: constipation, mechanical
  - Infection
    - ◆ prostate: prostatitis, prostate abscess
    - ◆ urethra: urethritis
    - ◆ periurethral gland abscess
  - Neurogenic
  - Pharmacologic
    - ◆ Alpha agonists (ephedrine, pseudoephedrine)
    - ◆ TCA/SSRI (imipramine)
    - ◆ β-antagonists: unmask/↑ □-tone
    - ◆ β2-agonists: striated muscle contraction
- Combined
  - Post-op
    - ◆ general
      - ♦ ↓ LOC & sensation
      - ♦ ↑ sympathetic tone → ↑ internal sphincter tone
      - ♦ pain → ↑ inhibitory reflex
    - ◆ anesthesia w/o catheter → bladder overdistention
      - ♦ ↑ SNA
      - ♦ detrusor ischemia
      - ♦ axonal degeneration
    - ◆ spinal anesthesia
    - ◆ pharmacologic
      - ♦ opioids: ↓ sensation → bladder overdistention, inhibition of sacral cord opioid receptors
    - ◆ traumatic urethral instrumentation
    - ◆ preexisting factors: bladder: functional/anatomic, outlet: functional/anatomic
- Women
  - Bladder
    - Infection/Inflam
      - ◆ infectious cystitis
      - ◆ non-infectious: IC, chemical
      - ◆ perivesical

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- Neurogenic
  - ◆ Causes of areflexia
    - ♦ MS
    - ♦ SB occulta
    - ♦ tethered cord
    - ♦ sacromyeloradiculitis: herpesvirus (zoster and simplex), CMV, EBV, HIV; Lyme disease
    - ♦ cauda equina/lumbar disc prolapse
    - ♦ anovesical inhibitory reflex (e.g. postop anal surgery, ?post-partum/episiotomy)
- Outlet
  - Mechanical BOO
    - ◆ intrinsic: urethral Ca, stricture, meatal stenosis, diverticulum, urethral prolapse, urethral caruncle, primary bladder neck obstruction, prolapsing ureterocele, lumenal (stone, clot, tumour)
    - ◆ extrinsic:
      - ♦ GI: constipation
      - ♦ gyne organs
        - \*\*pelvic organ prolapse\*\*
        - retroverted impacted uterus (1<sup>st</sup> trimester)
        - mass
          - malignancy: ovary, uterus, cervix
          - uterine fibroids
          - ovarian cyst
          - imperforate hymen
    - ◆ iatrogenic
      - ♦ \*\*failed anti-incontinence surgery\*\*
  - Infection: skenes gland abscess, urethritis
  - Neurogenic: sacromyeloradiculitis
- Combined
  - \*\*Dysfunctional voiding\*\*
    - ◆ STS: dysfunctional voiding/Fowler's syndrome/pseudomyotonia/Hinman's
    - ◆ SMS: 1° BN obstruction
  - Postop
  - Psychogenic
- Children
  - Outlet
    - Mechanical intrinsic
      - ◆ congenital: PUV, AUV, urethral polyp, urethral atresia, lacuna magna
      - ◆ acquired: labial adhesions, recent traumatic cath/instrumentation, urethral stricture
      - ◆ neoplastic: rhabdomyosarcoma, sarcoma botyroides, teratoma
    - Mechanical extrinsic: constipation, hydrometrocolpos
    - Inflam/Infec
    - Pharmacologic
  - Bladder
    - Infection/Inflam: cystitis (bacterial, viral)
    - extrinsic: perirectal abscess, appendicitis
    - Neurogenic
    - MMC
    - Pharmacologic
    - Metabolic
    - Hypermagnesemia (?moa)
    - Voluntary overdistention
  - Combined
    - Postop
    - Dysfunctional voiding/elimination

### How can one treat postoperative urinary retention?

- bladder decompression x 18-24h postop
- $\alpha$ -blockade

### How do the following disorders affect voiding function?

- hyperthyroidism

## Chapter 26 Questions - Voiding dysfn management.doc

- sympathetic overactivity → reduced flow rate and increased bladder capacity due to inhibitory  $\beta$ -adrenergic activity on detrusor muscle contractility
- schizophrenia
  - involuntary bladder contractions
- gastroparesis
  - abnormal detrusor contraction and delayed sensation
  - frequency, difficulty emptying
- myasthenia gravis
  - autoimmune disease caused by autoAb to ACh nicotinic receptors
  - leads to neuromuscular blockade and weakness in striated muscle
  - UI after TURP more common in this disease
  - hyperreflexia, hyporeflexia, urgency, UI
- Isaacs' syndrome
  - neurologic disorder characterized by continuous muscle contraction, fasciculations, myokymia, excessive sweating, and elevated creatinine kinase levels
  - due to Ab against  $K^+$  channels on peripheral nerves
  - retention
- Wernicke's encephalopathy
  - deficiency of thiamine: get peripheral neuropathy
  - involuntary contractions, decreased capacity
- adrenomyeloneuropathy
  - spastic paraparesis-type disorder, along w/ adrenal insufficiency
  - accumulation of long chain fatty acids
  - slowly progressive myelopathy w/ peripheral neuropathy and hypogonadism
  - variable LUTS, DHIC
- scleroderma
  - hesitancy, weak stream, frequency, nocturia, areflexia, decreased compliance
- Ehlers-Danlos syndrome
  - bladder diverticulae, VUR
- myotonic dystrophy
  - AD hereditary disorder characterized by myotonia and distal muscle atrophy, cataracts, endocrine disturbances, MR, dementia, testicular atrophy, infertility, alopecia, cardiac conductance disturbances
  - no characteristic patterns
- radiation
  - filling/storage sx: reduced capacity, reduced compliance → return to normal in 6/12
- aging
- endometriosis
  - LUTS, SP pain, UI, dyspareunia, dysuria
  - **use hormone manipulation if bladder involvement is small as 1<sup>st</sup>**
  - diffuse disease or disease w/ large vesical lesions: require OR

### What are the goals in management of voiding dysfunction?

- preserve/improve upper GU tract
- absence/control UTI
- storage at low Pves
- emptying at low Pdet
- adequate control
- no catheter/stoma
- social acceptability and adaptability
- vocational acceptability and adaptability

### What are the reasons to change/augment a given regimen?

- upper tract deterioration
- recurrent UTI
- lower tract deterioration
- inadequate storage
- inadequate emptying
- inadequate control
- unacceptable side effects
- skin changes due to collecting device

## Chapter 26 Questions - Voiding dysfn management.doc

### What are the pt factors to consider in choosing therapy?

- prognosis of disease
- general health
- inability to perform certain tasks: hand dexterity, habitus
- mental status
- motivation
- desire to remain catheter/appliance free
- desire to avoid surgery
- sexual activity status
- reliability
- educability
- psychosocial environment, interest, reliability, cooperation of family
- economic resources

### What is involved in behavioural therapy to facilitate urine storage?

- BEHAVE: for both bladder and outlet
  - can cause significant reduction in # of incontinence episodes or amount of urine lost: 40-80%
- Bladder retraining
  - timed voiding, gradually increasing intervals
  - **must always combine medical therapy w/ bladder retraining**
- Education
  - what accounts for urine volume, what is normal
- Habits: lifestyle changes and dietary modification
  - fluid limitation, avoid irritants
- Asked/prompted voiding + scheduled toileting
  - for mentally challenged ppl
- Voiding diary
- Exercises: pelvic floor physiotherapy
  - PFM exercises: quick flicks
  - vaginal cones
  - biofeedback
  - electrical stimulation
  - extracorporeal pelvic floor exercises
- biofeedback

### How do anticholinergics affect voiding function and behaviour?

- volume to 1<sup>st</sup> involuntary contraction increased
- amplitude of contraction decreased
- total bladder capacity increased
  - may be due to ongoing ACh-mediated stimulation of detrusor tone
- **"warning time" not increased**
- compliance not altered by anticholinergics
- outlet resistance not affected

### What is meant by "atropine resistance?"

- anticholinergics usually improve pts w/ involuntary contractions, but only partial inhibition results
- atropine only partially antagonizes response of bladder to stimulation
- major portion of NT involved in final common pathway to contraction is due to NANC neurotransmitter

### Where do the different muscarinic receptors exist?

- M1: smooth muscle, glands, brain
- M2: heart, brain, smooth muscle
  - predominant subtype
  - also involved in bladder contraction
- M3: brain (cortex, hippocampus), glands, sympathetic ganglia
  - primarily responsible for bladder contraction
- M4: basal forebrain, striatum
- M5: substantia nigra

## Chapter 26 Questions - Voiding dysfn management.doc

### Through what mechanism is the M2 receptor thought to be involved in bladder contractility?

- activation of M2 receptor leads to inhibition of adenylyl cyclase
  - prevents sympathetic increase in cAMP levels and bladder relaxation
- may also activate nonspecific cation channels, Rho proteins, and inactivation of K<sup>+</sup> channels

### What purely anticholinergic drugs have been used to facilitate urine storage?

- propantheline (Pro-Banthine) 15-30mg PO q4-6h
  - nonselective muscarinic antagonist
  - direct in vitro antimuscarinic binding potential approximates atropine better than all other drugs
  - **recommended** by Committee on Pharmacologic Tx of UI of the 1<sup>st</sup> International Consultation on Incontinence (ICI)
- atropine/dL-hyoscyamine (Cystospaz, Levsin)
  - rarely used due to s/e
- methantheline (Banthine)
  - higher ratio of ganglionic blocking to antimuscarinic activity than propantheline
- tolterodine (Detrol) 1-2mg PO BID
  - competitive muscarinic receptor antagonist
  - non-receptor selective, but shows bladder selectivity over salivary tissue
  - Appell: Detrol vs. Ditropan IR → no difference in efficacy, but tolerance better w/ Detrol
    - tolterodine 5 mg = oxybutynin 2 mg: ↓ incontinent episodes (50%), ↓ frequency (20%), ↑ voided volume
    - S/E: tolterodine < oxybutynin: ↓ dry mouth (freq and intensity), dose reductions and withdrawals
  - ditropan XL vs. detrol (OBJECT trial – OAB: Judging Effective Control and Treatment)
    - 10mg ditropan XL vs. 2mg Detrol
  - 2 RCTs compared Detrol vs. Ditropan s/e
    - Appell 2001: 12 week RCT double blind of overactive bladder oxybutynin XL vs. tolterodine IR
      - ◆ no significant difference in efficacy w/ similar incidence of S/E
    - Chapple 2001: small double blind randomized crossover in males to assess dry mouth using long-acting preparations – Detrol LA vs. Ditropan XL
      - ◆ efficacy Detrol LA 6 mg = Ditropan XL 20 mg, but ↓ dry mouth in Detrol arm
  - oxybutynin IR > oxybutynin XL ≥ tolterodine IR ≥ tolterodine LA
    - NB: these are *extrapolations* since as of 2001 only 2 RCT (Appell 2001, Chapple 2001) comparing oxybutynin and tolterodine have been performed
    - in general, tolterodine tested on anticholinergic-naïve Pts whereas ditropan XL tested on pts who tolerate IR formulation
  - **recommended** by ICI
- trospium chloride
  - quaternary ammonium compound
  - nonreceptor selective anticholinergic drug w/ mostly peripheral (antimuscarinic) effects, some ganglionic (nicotinic) effects
  - equally effective as Ditropan, fewer s/e
  - **recommended** by ICI
- darifenacin 10mg
  - highly selective M3 receptor antagonist
  - selectivity in some animal models for bladder over salivary glands
  - under investigation
- glycopyrrolate
- isopropamide
- anisotropine methylbromide
- methscopolamine
- homatropine

### What are the potential s/e of antimuscarinic agents?

- inhibition of salivary secretions
  - dry mouth
- blockade of the sphincter muscle of the iris and ciliary muscle of lens
  - pupillary dilation
  - paralysis of accommodation
  - blurred vision for near objects
  - photophobia
- tachycardia

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- drowsiness + cognitive dysfunction
- constipation: inhibition of gut motility
- anhidrosis: inhibition of sweat gland activity
- orthostatic hypotension
- ED: at high doses

### What are the contraindications for antimuscarinic agents?

- narrow angle glaucoma
- bladder outlet obstruction
- bowel obstruction
- cognitive impairment

### What anticholinergics w/ mixed actions have been used to facilitate urine storage?

- oxybutynin chloride (Ditropan) 5mg PO q6-8h
  - 3 major effects:
    - **potent muscarinic receptor antagonist**
    - **smooth muscle relaxant effects distal to cholinergic R (?CCB)**
    - **some local anaesthetic effects**
  - some selectivity for M3 and M1 receptors
  - higher affinity for muscarinic receptors in salivary gland
  - tertiary amine w/ first-pass effect: metabolite (N-desethyl oxybutynin) gives rise to most of its s/e
  - has been given PR and intravesically to prevent 1<sup>st</sup>-pass effect
  - **recommended** by ICI
- oxybutynin XL
  - OROS Osmotic Drug Delivery System
  - comparable efficacy and improved tolerability vs. Ditropan IR
- propiverine 15mg PO TID
  - antimuscarinic, direct smooth muscle relaxant effects, some local anaesthetic properties: like oxybutynin
  - similar efficacy and improved tolerability vs. Ditropan IR
  - **recommended** by ICI
- dicyclomine hydrochloride (Bentyl) 20mg PO TID
  - antimuscarinic effects, smooth muscle relaxant
- flavoxate (Urispas) 100-200mg PO q6-8h
  - no anticholinergic effects, moderate CCB activity, local anaesthetic properties, ability to inhibit phosphodiesterase
  - no effect on detrusor hyperreflexia
  - few s/e

### What CCBs have been used to facilitate urine storage?

- currently not an effective way to treat OAB
- terolidine 12.5mg PO BID: both CCB and anticholinergic effects
  - low concentrations: mainly anticholinergic effects
  - higher concentrations: calcium antagonist effects
  - side effects
    - **torsades de pointes in pts also on antidepressants or antiarrhythmics**
    - prolongation of AT and QTc intervals
    - bradycardia
  - **drug withdrawn** by manufacturer

### How do K<sup>+</sup> channel openers facilitate urine storage?

- relax various types of smooth muscle, including detrusor smooth muscle, by increasing K<sup>+</sup> efflux
  - results in membrane hyperpolarization
- no effect on normal bladder contraction
- ex: pinacidil, cromakalim → no evidence of efficacy, drugs withdrawn

### How do PG inhibitors facilitate urine storage?

- multiple mechanisms exist where PG synthesis inhibitors may decrease bladder contractility
- no evidence to support their use

### How do β-adrenergic agonists facilitate urine storage?

- β-receptor stimulation causes increase in bladder capacity

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- dose-related relaxant effect of  $\beta_2$ -agonists on bladder body, little effect on base or urethra
- terbutaline 5mg PO TID
  - few studies available
  - s/e: palpitations, tachycardia, tremor
- clenbuterol

### How do $\alpha$ -adrenergic antagonists facilitate urine storage?

- minimal if any contractile effects on *normal* detrusor smooth muscle
- contribution of these receptors changes in neurologic disease or injury
  - may be due to central effect
- parasympathetic decentralization leads to a marked increase in adrenergic innervation of the bladder
  - **conversion of usual beta (relaxant) response to alpha (contractile) effect in bladder**
  - urethral supersensitivity to  $\alpha$ -adrenergic stimulation in neurogenic bladder
- alpha blockade may decrease bladder contractility in pts w/ non-neurogenic voiding dysfunction as well
- $\alpha_2$  receptors are predominant adrenergic receptor overall in spinal cord
  - $\alpha_1$  receptors in cord are involved in bladder activation
  - beneficial effects of alpha blockade may be centrally acting

### How do TCAs facilitate urine storage?

- decrease bladder contractility and increase outlet resistance via 3 major pharmacologic actions:
  - **anticholinergic effects: central and peripheral**
  - **SNRI activity: block active transport uptake of NE and serotonin in presynaptic nerve ending**
  - **sedative effects: ?antihistaminic properties**
  - may also have direct smooth muscle relaxant effects via CCB activity
- imipramine (Tofranil) 25-100mg PO OD (10-50mg PO OD in kids)
  - prominent systemic anticholinergic effects, weak antimuscarinic effects on bladder smooth muscle
  - direct NANC inhibitory effect on bladder smooth muscle → may be interference w/  $\text{Ca}^{2+}$  movement and binding
    - exact mechanism unknown
    - may be increased serotonin concentration in spinal cord, w/ direct inhibition of normal excitatory pathways or depression of afferent ascending pathways
  - increases outlet resistance via  $\alpha$ -agonist effect in smooth muscle of bladder base and proximal urethra
  - may use in childhood nocturnal enuresis
  - **recommended** by ICI
- doxepin (Sinequan) 50mg PO qhs
  - more potent than other TCAs w/ respect to antimuscarinic and smooth muscle relaxant activity
- duloxetine
  - nearly equal effect on serotonin and NE uptake
  - no binding affinity for NT receptors
  - suppresses bladder activity through central serotonin receptor mechanisms

### What are the s/e of TCAs?

- anticholinergic side effects
  - inhibition of salivary secretions
    - dry mouth
  - blockade of the sphincter muscle of the iris and ciliary muscle of lens
    - pupillary dilation
    - paralysis of accommodation
    - blurred vision for near objects
    - photophobia
  - tachycardia
  - drowsiness
  - cognitive dysfunction
  - inhibition of gut motility
  - inhibition of sweat gland activity
  - orthostatic hypotension
  - ED: at high doses
- allergic phenomena
  - rash, hepatic dysfunction, obstructive jaundice, agranulocytosis
- CNS side effects
  - weakness, fatigue, sedation
  - Parkinsonian effects, tremor



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- manic/schizophrenic s/e
- postural hypotension
- excess sweating: unknown etiology
- delay of orgasm or anorgasmia: unknown etiology
- **arrhythmias, interaction w/ other medications → consult Cardiology if needed**

### What are the contraindications to taking TCAs?

- MAOIs
  - severe CNS toxicity: hyperpyrexia, seizures, coma
- elderly
  - significant s/e: weakness, fatigue, postural hypotension
  - increased risk of falls and hip #

### How does DMSO facilitate urine storage?

- dimethyl sulfoxide
- multiple pharmacologic actions (membrane penetrant, anti-inflammatory, local analgesic, bacteriostatic, diuretic, cholinesterase inhibitor, collagen solvent, vasodilator)
- not useful in tx of detrusor hyperreflexia or instability, or in any pt w/ LUTS w/o IC

### How do polysynaptic inhibitors facilitate urine storage?

- baclofen (Lioresal)
  - decrease outlet resistance secondary to DESD
  - GABA<sub>B</sub> agonist
  - depresses monosynaptic and polysynaptic motoneurons and interneurons in spinal cord

### What medications have been used to decrease sensory input to facilitate urine storage?

- vanilloids → stimulate and desensitize unmyelinated C fibers to produce pain and release neuropeptides
  - activate sensory fibers through ion channel: **vanilloid receptor subtype 1 (VR1)**
  - nonselective cation channel, limited selectivity for calcium
  - induce analgesia via downregulation of substance P, upregulation of NOS, VIP, galanin
  - not yet approved
- capsaicin 1-2mM x 30min
  - irritant and algogenic compound from hot red peppers
  - highly selective effects on subset of sensory neurons: polymodal R and warm thermoreceptors
  - opens cation-selective ion channel VR1 (vanilloid receptor subtype 1), allowing Ca<sup>2+</sup>/Na<sup>+</sup> influx that depolarizes neuronal pain fibers
  - antinociceptive and anti-inflammatory action after initial algogenic effect
  - lack of systemic s/e, no long-term adverse effects
  - motor fibers not affected
- resinaferatoxin (RTX) is ultrapotent analogue
  - from cactus-like plant *Euphorbia resinifera*
  - is a vanilloid: ultrapotent analogue of capsaicin → 1000X more potent w/ minimal initial excitatory effect
  - currents induced by resinaferatoxin develop slowly and are more sustained
    - causes desensitization without previous stimulation
  - both meds should only affect small unmyelinated afferent C fibers
    - micturition reflex stimulated by A-delta myelinated fibers should not be affected
  - difference due to receptor gating → RTX opens channel after initial delay, then provokes persistent currents
  - slowly increasing intracellular calcium levels not enough to cause AP formation
  - may inhibit TTX-insensitive sodium channels involved in AP generation
- tachykinin receptor blockade: no meds yet

### How does the use of Botox facilitate urine storage?

- Botox 200-300 units injected at 20-30 sites (10 units/ml/site) sparing the trigone (to prevent VUR)
  - inhibits ACh release at NMJ
- improved continence, increased capacity, decrease in max Pdet
- no adverse s/e other than UTI
- duration of paralysis 3-9 months, return to baseline

### What is the mechanism by which bladder overdistension facilitates urine storage?

- prolonged distension using hydrostatic pressure equal to systolic blood pressure

## **Chapter 26 Questions - Voiding dysfn management.doc**

- improvement attributable to ischemic changes in the nerve endings or terminals in bladder wall
- little use in pts w/ neurogenic detrusor hyperreflexia

### **What are the complications of bladder overdistension?**

- bladder rupture (5-10%)
- hematuria
- retention

### **What methods of electrical stimulation can be used to facilitate urine storage?**

- sacral neuromodulation
- common peroneal or posterior tibial nerve patch electrode stimulation
- transcutaneous stimulation of the thigh muscle
- noninvasive magnetic stimulation of the sacral nerve roots
- transurethral electrical bladder stimulation (TEBS)

### **What are the requirements for successful use of electrical stimulation and neuromodulation to inhibit bladder contractility?**

- cooperative pt
- preservation of GU tract morphology
- preservation of sacral spinal cord "reflex centre"
- low degree of peripheral denervation of the striated floor muscles
- ability to perform CIC

### **What are the potential mechanisms involved in the inhibition of pelvic nerves via neuromodulation?**

- inhibitory pudendal to pelvic nerve reflex
- pudendal to hypogastric nerve reflex
- sympathetic inhibition of parasympathetic ganglionic cell transmission
- $\beta$ -adrenergic effect on smooth muscle of bladder

### **What frequencies have been used in neuromodulation?**

- 5-10Hz: inhibition of bladder contractility
- 20-50Hz: increase outlet resistance
- delivered below sensory threshold

### **What are the different stages of neuromodulation?**

- acute sacral modulation: test needle
- subchronic neuromodulation: test for 4-7days w/ perc electrode and external stimulator
- chronic sacral neuromodulation: permanent implantation

### **Which pts best benefit from sacral neuromodulation?**

- pts most likely to benefit have detrusor hyperactivity or detrusor hypocontractility
- pts w/ pain syndromes less likely to benefit

### **What are the potential mechanisms that acupuncture may facilitate urine storage?**

- endorphinergic effects at the sacral cord level
- inhibitory somatovesical effects
- increases in peripheral circulation

### **What methods of bladder denervation have been used to facilitate urine storage?**

- more selective but less effective as move from central → peripheral
- Very central
  - subarachnoid block
    - converts severe spasticity to flaccidity and abolish autonomic hyperreflexia
    - requires CIC
    - lack of selectivity (unintended motor loss), ED very common
- Less central
  - sacral rhizotomy
    - converts hyperreflexic bladder to areflexic bladder
    - adversely affects rectum, anal, urethral sphincters, sexual function, and lower extremities
  - selective sacral rhizotomy

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- 3<sup>rd</sup> anterior (ventral) sacral root provides dominant motor innervation to bladder → abolish this only
- may abolish reflex UI, improve compliance, and abolish DESD
- Peripheral
  - transvaginal partial denervation of the bladder
  - cystolysis
    - extensive perivesical dissection and mobilization w/ division of the superior vesical pedicle and the ascending branches of the inferior vesical pedicle
  - bladder transection
    - complete circumferential division of full thickness of bladder wall at level just above trigone
    - success rate 65%
  - transvesical infiltration of the pelvic plexus w/ phenol → chemical neurolysis
    - s/e: retention, vaginal fistulae
- all procedures abandoned → 100% relapse rate by 18mo

### How do $\alpha$ -adrenergic agonists affect the bladder outlet to facilitate urine storage?

- bladder neck and proximal urethra contain many  $\alpha_1$ -receptors, which produce smooth muscle contraction when stimulated
- $\alpha_{1A}$  subtype predominate in GU tract
- $\alpha_{1L}$  thought to mediate phenylephrine-mediated contractions in urethra

### What are the s/e of $\alpha$ -adrenergic agonists?

- hypertension
- anxiety
- insomnia
- headache
- tremor
- weakness
- palpitations
- cardiac arrhythmias
- respiratory difficulties
  - use w/ caution in pts w/ htn, CVS disease, or hyperthyroidism

### What $\alpha$ -adrenergic agonists have been used to increase outlet resistance to facilitate urine storage?

- ephedrine 25-50mg PO QID, pseudoephedrine (stereoisomer) 30-60mg PO QID
  - noncatecholamine sympathomimetic that enhances NE release from sympathetic neurons and stimulates both  $\alpha$  and  $\beta$  receptors
  - little benefit in severe SUI
- phenylpropanolamine/PPA (Ornade) 25-75mg
  - blood pressure elevation and **risk of hemorrhagic stroke 16X higher in women** → taken off market
- midodrine 5-10mg OD
  - selective  $\alpha_1$ -adrenergic agonist → no improvement

### What SNRIs have been used to increase outlet resistance to facilitate urine storage?

- imipramine, duloxetine
  - increase in urethral resistance may be expected if enhanced  $\alpha$ -adrenergic effect produced due to NE uptake inhibition

### What $\beta$ -blockers and $\beta$ -agonists have been used to increase outlet resistance to facilitate urine storage?

- terbutaline, clenbuterol (selective  $\beta_2$  agonist)
  - beta agonists, generally felt to decrease urethral pressure
  - may increase contractility of fast-contracting striated muscle fibers, increasing urethral pressures
- propranolol 10mg PO QID:  $\beta$ -blocker
  - success in few pts

### How do estrogens effect urine storage?

- increases sum total of factors contributing to urethral outlet resistance
  - ↑ # and sensitivity of alpha receptors, ↑ NOS, ↑ blood flow

### What vaginal and perineal occlusive and supportive devices have been used to facilitate urine storage?

- support devices

## **Chapter 26 Questions - Voiding dysfn management.doc**

- pessary → reduce vaginal prolapse and support interior vaginal wall
  - work best in ppl w/ minimal leakage, elderly woman w/ severe prolapse and is a poor surgical candidate
- occlusive devices
  - external devices
    - penile clamp: risky in pts w/ neurologic disease and sensory impairment → tissue damage
  - internal devices

### **What are the characteristics of an ideal occlusive/supportive device?**

- efficacy
- comfort
- ease of use
- lack of interference w/ voiding
- lack of tissue damage
- lack of infection
- no compromise of subsequent tx
- cosmetic appearance
- lack of interference w/ sex

### **What pts are ideal for use of an external occlusive/supportive device?**

- mild/moderate pure sphincteric UI
- no significant bladder overactivity or decreased compliance
- desires active involvement
- desires immediate results
- body habitus, manual dexterity, and cognitive ability to use

### **What are the reasons for failure of an external occlusive/supportive device for UI?**

- reluctance to put anything inside
- inconvenience
- discomfort
- fear of infection
- nonwillingness to pay
- perceived lack of success
- nonincentive by MD

### **What are the indications for BN closure?**

- totally incompetent outlet that is uncorrectable by medical or conventional surgical means
  - urethral necrosis due to long-term cath in neurologically impaired woman
  - trauma
  - infection
  - fibrosis

### **What problems were associated w/ myoplasty for functional sphincter reconstruction?**

- need uncomfortable prolonged adduction of leg to maintain continence
- unsatisfactory sustained muscle contraction
- loss of resting tension
- passive obstruction
- risk of fibrosis

### **What is the role of DDAVP in facilitation of urine storage?**

- DDAVP 20-40ug intranasally
  - suppresses urine production for 7-12hrs
- Indications
  - DI
  - nocturnal enuresis
  - nocturnal sx and spot usage during the day

### **What are the side effects of DDAVP?**

- risk of hyponatremia → must prevent excess fluid intake
- abdo pain, N/V, headache, epistaxis

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### What are the contraindications to using DDAVP?

- CHF
- hypertension
- liver disease
- Crohn's disease
- primary polydipsia

### What are the requirements for a pt to start CIC?

- cooperative, well-motivated pt or family
- adequate hand control or willing family member
- adequate urethral exposure

### What are the complications of catheterization?

- CIC
  - false passages
  - bladder perforation
  - silent deterioration of upper tracts
  - UTI
- Indwelling
  - bacteriuria
  - contracted fibrotic bladder
  - bladder stones
  - bladder spasm
  - BN erosion
  - bladder cancer: SCC

### Is long-term indwelling catheterization in the SCI population associated w/ a poorer outcome?

- controversial
  - Catheter Bad
    - Jacobs and Kaufman 1978: removal of UC in SCI men prevented renal deterioration
    - Hackler 1982: accelerated renal deterioration in SCI w/ long-term SP cath
    - McGuire 1984: poorer outcome in women w/ UC after 2-12 years vs. CIC
    - Weld 2000: complications in UC 55%, SPC 45%, spont. void 30%, CIC 30%
      - ◆ ?related to compliance: spont. void and CIC more likely to have N compliance and ↓ VUR, pyelo, upper tract stones
  - Catheter OK
    - Dewire 1992: incidence of renal and urinary tract complications no different ≥10 yrs
    - Chao 1993: SCI w/ UC vs. SPC vs. none (mainly condom) w/ ≥20 yrs f/u – ↑ renal scarring, but no other differences in renal function or other urologic complications
    - Jackson 1992: SCI women w/ UC followed up to 10 yrs vs. men w/ condom – no difference in upper vs. lower tract complications; renal function equal on renography
    - Barnes 1993: NGB w/ SPC w/ relatively short-term f/u – 40% blockage, recurrent Sx UTI 25%, urethral leakage in 50%
    - MacDiarmid 1995: SPC in SCI f/u 1-10 yrs – no renal deterioration, 40% bladder stones, 7% renal stones, 40% blockage, gross H/A 5%
    - Sheriff 1998: 185 w/ NGB w/ SPC mean 24 months; mostly failed CIC; about 5% complications of bowel injury w/ insertion, bleeding, displacement; bacteriuria in 100%, recurrent Sx UTI 5%, recurrent blockage 20%
    - Dmochowski 2000: risk of complications chronic indwelling 54%, SP 44%, voiding 32%, CIC 27%

### Should screening cystoscopy be performed in SCI pts w/ chronic indwelling?

- Yes
  - may result in an earlier stage of dx of bladder ca
  - all pts w/ new-onset hematuria should be evaluated

### What are the indications for supravescical diversion in pts w/ voiding dysfunction?

- rarely indicated: Cut It Out!
  - CIC impossible: intractable storage or emptying failure when CIC is impossible
  - Infections: recurrent urosepsis
  - Obstruction: progressive hydronephrosis and intractable upper tract dilation, may be due to UVJ obstruction from trabeculae

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### What are the complications of external urine collecting devices?

- no optimal external device for female
- pressure necrosis of the penis if impaired sensation
- inadequate penile length to maintain condom cath  
→ may need penile prosthesis
- lacerations of penile skin

### Which pts should use external compression (Credé) to decompress the bladder?

- pts w/ decreased bladder tone that can generate Pves > 50 cm H<sub>2</sub>O with a Crede, and have **borderline outlet resistance**

### How does one properly perform a Credé?

- place thumbs of each hand over area of ASIS
- all digits over SP area, slightly overlapped, press into abdomen
- press downward when behind symphysis as deeply as possible  
→ may also use closed fist or rolled-up towel

### What are the contraindications to external compression or Credé?

- some say it should never be used  
→ VUR
- pts w/ decentralization and decreased compliance  
➤ intravesical pressures may increase silently

### How can one use reflex contractions to facilitate bladder emptying?

- manual stimulation of certain areas within sacral and lumbar dermatomes  
→ pull skin/hair of pubis, scrotum or thigh  
→ squeezing clitoris  
→ DRE  
→ rhythmic SP manual pressure (7-8 pushes q3second) → most effective according to the classic reference (Glahn 1974)
- if DESD present, must find way to decrease outlet resistance

### What parasympathomimetics have been used to facilitate bladder emptying?

- bethanechol (Urecholine, Duvoid, others) 5-10mg SC  
→ relatively selective action on bladder  
→ acetylcholinesterase resistant  
→ used historically for post-op/post-partum AUR, only if pt awake and alert w/o BOO  
➤ pts w/ incomplete LMN lesions most likely to respond  
→ little to no evidence of success
- metoclopramide (Reglan)  
→ dopamine antagonist w/ cholinergic properties  
→ central antiemetic effect  
→ increases tone of LES, promoting gastric emptying
- cisapride (Prepulsid) 20mg PO TID  
→ associated w/ **life-threatening arrhythmias (QT prolongation)** → taken off market  
➤ in pts on meds that inhibit cisapride metabolism or prolongs QT interval

### What are the side effects of cholinomimetic drugs?

- flushing, N/V, diarrhea, GI cramps, bronchospasm, h/a, salivation, sweating, blurred vision (difficulty w/ visual accommodation)

### What are the contraindications to the use of cholinomimetics?

- bronchial asthma
- PUD
- bowel obstruction
- enteritis
- recent GI surgery
- cardiac arrhythmias
- hyperthyroidism
- BOO

## Chapter 26 Questions - Voiding dysfn management.doc

### How do prostaglandins facilitate bladder emptying?

- contribute to maintenance of bladder tone and bladder contractile activity
- may affect bladder muscle directly or indirectly through effects on neurotransmission
  - neuromodulators of NT
  - sensitization of sensory nerves
  - activation of sensory nerves
  - potentiation of ACh release from cholinergic nerve terminals through prejunctional PG receptors

### What prostaglandins are present in the human bladder?

- $PGE_2 > PGE_1 > PGF_{2\alpha} > TXA_2$

### What are the side effects of PG use?

- N/V, diarrhea, pyrexia, htn, hypotension

### How do opioid antagonists facilitate bladder emptying?

- endogenous opioids exert tonic inhibitory effect on voiding reflex
  - narcotic antagonists may stimulate reflex bladder activity
- little practical use

### How has bladder myoplasty been used to facilitate bladder emptying?

- transfer of innervated free striated muscle flap: rectus muscle

### How has electrical stimulation been used to facilitate bladder emptying?

- to the nerve roots
  - anterior nerve root stimulation w/ Brindley device
  - used in pts w/ inefficient or no reflex voiding after SCI
  - requires sacral rhizotomy to prevent simultaneous bladder and striated sphincter stimulation
    - eliminates reflex UI and improves low bladder compliance
  - requires bladder that can contract and intact neural pathways b/w sacral cord SPN and bladder
  - electrodes applied to S2-4 nerve roots
    - can stimulate either bladder (S3), rectum (S2-4), or erectile stimulation (S2 + small S3)
  - void via **post-stimulus voiding**
    - striated sphincter relaxes b/w pulses, voiding occurs in spurts at above normal bladder pressures
- directly to bladder or spinal cord: failure, not used
  - most effective in pts w/ hypotonic or areflexic bladders
  - failure due to fibrosis, electrode malfunction, bladder erosion, or other equipment malfunction
    - increase in Pdet generally not coordinated w/ BN opening
  - stimulus to other structures → stimulus thresholds are lower than the bladder
    - causes pain, defecation, leg contraction, or ejaculation
- TEBS
  - controversial treatment, limited clinical efficacy
  - establishes conscious control over initiation and completion of voiding reflex
  - used in incomplete central or peripheral nerve lesions → some nerve pathways preserve but are too weak
- neuromodulation
  - useful in pts w/ incomplete voiding and neurogenic chronic retention

### How can one classify the options available for decreasing outlet resistance?

| Obstruction | Behavioral/General | Medical/Pharmacologic  | Surgical/Invasive   |
|-------------|--------------------|--|---|
| Anatomic    |                    | 1) prostate-oriented <ul style="list-style-type: none"><li>a) <math>\alpha</math>-antagonists</li><li>b) 5 AR-inhibitors</li><li>c) LHRH agonists/antagonists</li><li>d) antiandrogens</li></ul> | 1) prostate/BN <ul style="list-style-type: none"><li>a) prostatectomy, TUIP</li><li>b) TUR BN</li></ul> 2) urethra <ul style="list-style-type: none"><li>a) stricture repair</li><li>b) stent</li><li>c) urethrolisis</li></ul> |
| Smooth S.   |                    | 2) $\alpha$ -antagonists <ul style="list-style-type: none"><li>a) doxazosin</li><li>b) tamsulosin</li><li>c) phenoxybenzamine</li></ul>  | 3) TUR/TUI BN<br>4) Y-V plasty  |

|                    |                                      |                           |                                |
|--------------------|--------------------------------------|---------------------------|--------------------------------|
|                    |                                      | d) prazosin               |                                |
|                    |                                      | e) terazosin              |                                |
|                    |                                      | 3) $\beta$ -agonists      |                                |
| <b>Striated S.</b> | 1) behavioral therapy $\pm$ feedback | 4) medical sphincterotomy | 5) sphincterotomy              |
|                    | 2) psychotherapy                     | a) Botox                  | 6) urethral stent              |
|                    |                                      | b) $\alpha$ -antagonists  | 7) urethral overdilation       |
|                    |                                      | c) benzo's                | 8) pudental nerve interruption |
|                    |                                      | d) baclofen               |                                |
|                    |                                      | e) dantrolene             |                                |

**How has pharmacologic therapy been used to decrease resistance at smooth sphincter to facilitate voiding?**

- smooth muscles of bladder base and proximal urethra contain predominantly  $\alpha$ -adrenergic receptors
  - $\beta$  receptors are present
  - $\alpha_2$  receptors more common, but  $\alpha_1$  receptors mediate smooth muscle contraction
  - $\beta$  receptors more common in bladder body, but  $\alpha$  receptors present
- tonic sympathetic stimulation of  $\alpha$ -receptors controls sphincter
  - $\alpha$  blockade exert effects by affecting smooth muscle of BN and proximal urethra
  - $\alpha$  blockade **may decrease striated sphincter tone as well**
  - may decrease bladder contractility
- phenoxybenzamine (Dibenzylamine) 10-20mg PO OD
  - irreversibly blocks both  $\alpha_1$  and  $\alpha_2$  receptors: effects last for several days
  - side effects
    - orthostatic hypotension
    - reflex tachycardia
    - nasal congestion
    - diarrhea, N/V
    - miosis
    - sedation
    - peritoneal sarcomas and lung tumours
- phentolamine
  - nonspecific alpha blocker
- prazosin (Minipress) 2-20mg PO OD
  - 1<sup>st</sup> potent selective  $\alpha_1$  blocker
  - "first dose phenomenon"**: faintness, dizziness, palpitation, syncope  $\rightarrow$  due to acute postural hypotension
    - restrict initial dose to 1mg
- terazosin (Hytrin) 1-10mg PO OD
  - selective  $\alpha_1$  blocker
  - more common dizziness and asthenia
- doxazosin (Cardura)
  - selective  $\alpha_1$  blocker
  - more common dizziness and asthenia
- tamsulosin (Flomax) 0.4mg PO OD
  - selective  $\alpha_1$  blocker
  - once daily w/o titration
  - more common retrograde ejaculation and rhinitis
- alfuzosin (Xatral) 10mg PO OD: selective  $\alpha_1$  blocker

**What is the indication for TUIBN?**

- demonstration of true obstruction at BN or proximal urethra by video UDS or UPP

**How does one perform a TUIBN?**

- incision of BN at either 5 or 7 o'clock
  - single full-thickness incision from bladder base to level of verumontanum

**How has pharmacologic therapy been used at the level of the striated sphincter to facilitate bladder emptying?**

- no class of pharmacologic agents exists that will selectively relax striated muscles of pelvic floor
  - GABA and glycine are major inhibitory NTs in CNS  $\rightarrow$  3 types of receptors:
    - GABA<sub>A</sub>: binding sites for benzos, barbs, neurosteroids, EtOH
    - GABA<sub>B</sub>: activated by baclofen
    - GABA<sub>C</sub>: may be a subset of A
- benzodiazepines



## Chapter 26 Questions - Voiding dysfn management.doc

- potentiate the action of GABA by facilitating neurotransmission through the GABA<sub>A</sub> receptor
- s/e: CNS depression (sedation, lethargy, drowsy, slowing of thought processes, ataxia)
- diazepam not effective
- may be worth trying if no neurologic disease, w/ inadequate relaxation of the pelvic floor striated muscles
- baclofen (Lioresal) 5-20mg PO BID-QID
  - depresses monosynaptic and polysynaptic excitation of motoneurons and interneurons in the spinal cord by activating GABA<sub>B</sub> receptors
  - primary site of action in cord
  - s/e: drowsiness, insomnia, rash, pruritis, dizziness, weakness, inability to walk/stand
    - do not use in pts w/ spasticity from cerebral lesions
  - withdrawal: hallucinations, anxiety, tachycardia
  - cannot cross the blood-brain barrier: intrathecal delivery by implanted infusion pump may help
- dantrolene (Dantrium) 25-400mg PO OD
  - direct peripheral action on skeletal muscle
  - inhibits the excitation-induced release of calcium ions from the SR of striated muscles, inhibiting excitation-contraction coupling and diminishing the mechanical force of contraction
  - can improve voiding in pts w/ classic DESD
    - virtually nobody uses this
  - s/e: weakness, euphoria, dizziness, diarrhea, hepatotoxicity, hepatitis
- botulinum toxin (Botox) 150 IU, 4 pt injection into EUS
  - inhibits ACh release at the NMJ of somatic nerves on striated muscle
  - duration 2-9mo
- α-bungarotoxin: venom of Formosan snake, blocks nicotinic receptors in ganglia

### What is the primary indication for surgical sphincterotomy?

- DESD in the male pt when other types of management are unsuccessful or are not possible
- improvement in 70-90%
- external collecting device

### How does one perform a surgical sphincterotomy?

- 12 o'clock incision
  - main muscle bulk is anteromedial
  - blood supply primarily lateral → little chance of hemorrhage
- incision should extend from verumontanum to at least bulbomembranous junction

### What are the complications of surgical sphincterotomy?

- hemorrhage (5-20%)
- erectile dysfunction (5%)
- early failure: due to inadequate procedure, inadequate detrusor function, or BN/prostatic obstruction
- late failure: due to fibrosis

### What parameters can be used to judge success of sphincterotomy?

- **DLPP: most reliable UDS parameter to predict risk of upper tract deterioration**
  - DLPP > 40cmH<sub>2</sub>O = sphincterotomy failure (Kim 1998)
- upper tract function (Cr, US)
- presence/severity of VUR
- frequency and severity of autonomic hyperreflexia
- urosepsis occurrence
- need for CIC
- PVR
- sexual function

### How has urethral overdilation been used to facilitate bladder emptying?

- dilation to 40-50F in females → same as sphincterotomy in men
- balloon dilation of EUS to 90F at 3atm !!!
- **ineffective for long-term tx of DESD**

### How have urethral stents been used to facilitate bladder emptying?

- Urolume stent
  - decreases DLPP and PVR

### **Chapter 26 Questions - Voiding dysfn management.doc**

- as effective, less morbid, and less expensive than sphincterotomy
- decreases mean voiding pressure
- potentially reversible

#### **What are the complications of the Urolume?**

- stent migration
- BN obstruction

#### **Why are pudendal nerve interruptions not used to facilitate bladder emptying?**

- very high rate of ED
- fecal and severe SUI





## **Chapter 27**

### **• Urinary Incontinence: Pathophysiology, Evaluation, Medical Management •**

---

#### **What are the properties of the bladder and sphincter that promote continence?**

- Bladder
  - Accommodation: Pdet remains constant during filling
  - Compliance
  - Capacity
  - Neural Control
- Sphincter
  - Coaptation: watertight mucosal seal, inner wall softness
  - Compression: extracellular matrix, collagen, elastin, urethral smooth muscle, urethral striated muscle
  - Anatomic support: transmission of Pabd
  - Neural control

#### **What are the sphincteric supports in the female?**

- levator ani muscle complex forms a hammock
- 2 leaves of fascial covering
  - endopelvic fascia: abdominal side
  - pubocervical fascia: vaginal side
  - both fuse laterally to insert along the tendinous arc fasciae pelvis
- pubourethral ligaments: extend from urethra to pubis
  - may be 2 separate structures: one at BN, one distally
- anterior vaginal wall: supports urethra by lateral attachment to levators
- urethropelvic ligaments from suburethral fascia at BN and proximal urethra to levators and arcus tendineus
  - separate from hammock

#### **What is the first recorded event in the micturition reflex?**

- sudden and complete relaxation of the striated sphincteric muscles
  - complete electrical silence of the sphincter EMG

#### **What is the ICS definition of urinary incontinence?**

- involuntary loss of urine that is objectively demonstrable and is a social or hygienic problem

#### **What is the difference b/w detrusor hyperreflexia and detrusor instability?**

- detrusor hyperreflexia: due to neurologic disorder
- detrusor instability: involuntary detrusor contraction not due to neurologic disorders

#### **How can one classify sphincteric incontinence?**

- urethral hypermobility
  - weakness of pelvic floor support
    - urethra normally compressed on hammock-like musculofascial layer
    - SUI occurs if this supporting layer is lost
  - rotational descent of the BN and proximal urethra during increase in IAP
  - anterior wall of urethra may remain fixed while posterior wall moves during stress → pulls open the urethral lumen
- ISD = intrinsic malfunction of the urethral sphincter itself

#### **What are the causes of ISD?**

- previous pelvic surgery: slings, urethral diverticulectomy, TAH, APR, VIU, TUIBN
  - ISD present in 75% if 2 or more failed anti-incontinence procedures
- neurologic conditions: MMC, anterior spinal artery syndrome, lumbosacral neurologic conditions, Shy-Drager
  - **radiation**: damages mucosal seal coaptation of the urethra, + local neurologic damage

## Chapter 27 Questions - UI.doc

- aging
- hypoestrogenic state
  - urethral mucosa and submucosal spongy layer under hormonal control
  - estrogen deficiency leads to atrophy of the spongy tissue and flattening of the epithelium

### How does one classify SUI?

- Blaivas and Olsson (1988)
  - based on 2 parameters: LPP and Q-tip angle
- Type 0
  - pt complains of SUI, but no incontinence demonstrable
  - BN and urethra closed at rest, at or above lower end of pubis
  - during stress, BN and proximal urethra descend and open like type I and II
- Type I
  - BN closed at rest, situated above lower end of pubis
  - during stress, BN and urethra open and **descend < 2cm**
  - UI is apparent
  - small or no cystocele
- Type IIa (above pubis)
  - BN closed at rest, above lower end of pubis
  - during stress, BN and urethra open w/ **rotational descent** characteristic of a cystocele
  - UI is apparent
- Type IIb (below pubis)
  - BN and urethra closed at rest, at or **below lower end of pubis**
  - during stress, may not be further descent, but proximal urethra opens and UI occurs
- Type III
  - BN and proximal urethra are open at rest in absence of contraction
  - proximal urethra no longer functions as a sphincter

### What are the RF for urinary incontinence?

- Predisposing Factors
  - gender: women
  - genetic predisposition
  - race: whites > blacks
  - collagen: less supportive collagen subtypes
  - anatomic/neurologic factors: childbirth, surgery, pelvic nerve/muscle damage, radiation
- Promoting Factors
  - nutrition
  - obesity
  - smoking
  - activity level
  - toilet habits
  - fluid intake
  - medications
  - **pregnancy**: increased risk of perineal and vaginal trauma w/ forceps
- Decompensating factors
  - aging
  - physical and mental well-being
  - environment
  - medications

### What are the causes of transient incontinence in the elderly?

- **Mnemonic - DIAPPERS**
  - Delirium
  - Infection
  - Atrophic Vaginitis / Urethritis
  - Pharmaceuticals
  - Psychological problems
  - Excess urine output
  - Restricted mobility
  - Stool impaction

## Chapter 27 Questions - UI.doc

### What are the causes of detrusor overactivity?

- Detrusor hyperreflexia
  - Supraspinal lesion
    - stroke
    - Parkinson's
    - Hydrocephalus
    - Brain tumour
    - MS
  - Suprasacral lesion
    - SCI
    - MS
    - spina bifida
    - transverse myelitis
- Detrusor instability
  - BOO
  - postsurgical
  - bladder stones
  - bladder tumour
  - UTI
- Idiopathic

### Where must a neurologic lesion be located to cause DESD?

- between the brain stem (pontine micturition centre) and sacral spinal cord (sacral micturition centre)

### What are the causes of decreased bladder compliance?

- Neurogenic
  - myelodysplasia
  - Shy-Drager syndrome
  - thoracolumbar SCI
  - TAH
  - APR
- Increased collagen
  - TB cystitis
  - radiation cystitis
  - IC
  - chronic indwelling catheter
  - prostatic obstruction

### What are the urethral wall factors that promote continence?

- wall tension or external compression
- inner wall softness
- filler material beneath mucosa

### What are the mechanisms of external compression of the urethral lumen?

- smooth and striated muscle tone
- phasic contractions of the smooth and striated musculature
- elastic and viscoelastic properties of the extracellular matrix
- mechanical factors related to pressure transmission of abdo pressure
- structural support of the posterior urethral wall

### What are the causes of loss of urethral compression and support?

- Loss of urethral compression
  - Neurologic
    - anterior spinal artery syndrome
    - radical pelvic surgery
    - myelodysplasia
    - hypoenestrogenic states
    - aging
  - Anatomic

## Chapter 27 Questions - UI.doc

- scarring post urethral surgery
- Loss of urethral support
  - levator (hammock) hypothesis
  - childbirth
  - trauma
  - pelvic surgery
  - hypoestrogenic states
  - aging

### What is involved in the diagnostic evaluation for incontinence?

- History
  - Events before sx are noted
    - GU history
      - ◆ voiding habits
      - ◆ childhood enuresis
      - ◆ UTI
    - Gyne/Obstetric hx: GxPx
    - PMHx
      - ◆ VUR, stones, previous GU surgery
      - ◆ neurourologic conditions: congenital, metabolic, traumatic, degenerative
      - ◆ low back pain, previous spinal cord injury/surgery, Parkinson's, MS, stroke
    - Meds
      - ◆ sympatholytics: clonidine, phenoxybenzamine, Hytrin, doxazosin
      - ◆ anticholinergics
      - ◆ sympathomimetics: TCAs, ephedrine, imipramine, Sudafed
      - ◆ diuretics
      - ◆ estrogen replacement
    - Allergies, EtOH, smoking, drugs
    - FHx: epilepsy, Huntington's, degenerative conditions
  - Current symptoms
    - GU sx
      - ◆ LUTS
        - ◆ voiding sx: hesitancy, slow stream, intermittency, straining, PVD, sensation incomplete emptying
        - ◆ storage sx: frequency, nocturia, urgency
      - ◆ incontinence: pattern, severity, frequency, cause
        - ◆ why voiding occurs: urge, convenience, attempt to prevent UI
        - ◆ how long can she go comfortably between urinations
        - ◆ how long micturition can be postponed once she gets the urge
        - ◆ **bother**
        - ◆ pads: #, changing
        - ◆ triggers for UI: running water, positional changes, key in front door
        - ◆ SUI: cough, sneeze, lifting
        - ◆ overflow UI
        - ◆ unconscious UI: w/o any obvious increase in IAP, urge, or conscious recognition that leakage is occurring
        - ◆ continuous UI: constant leakage
      - ◆ UTI, hematuria
    - GI Sx
      - ◆ constipation, fecal incontinence
      - ◆ change in BM
    - Neurologic sx: visual changes, sensory changes, motor weakness, gait abnormalities
    - Sexual and bowel dysfunction
      - ◆ sensory alterations in genital/perianal area
      - ◆ ED, ejaculatory disorders
  - Adjuncts to history
    - Pt questionnaire
      - ◆ duration and time course of LUTS
      - ◆ AUA sx index / IPSS
        - ◆ 7 sx, scored 0-5: mild sx (0-7), moderate (8-19), severe (20-35) + QOL index (0-5)
        - ◆ IPSS does not correlate w/ presence of detrusor instability or BOO

## Chapter 27 Questions - UI.doc

- ♦ symptomatic pts w/ BOO do not have different scores from pts w/o obstruction that have detrusor dysfunction
- ♦ ICSmale questionnaire
- Voiding diary: 3-5days
  - ♦ 24h urine output, # voids, voiding interval, diurnal distribution, timing and triggers for UI, functional bladder capacity
  - ♦ more reliable than pt's hx → no correlation b/w # voids via history compared w/ voiding diary
- Pad test → always ask if results are representative of normal function
  - ♦ wt of all pads/diapers used by pt for 24-48hrs while pt on Pyridium
  - ♦ **≤8 g over 24 h or ≤2 g over 1 h considered normal**
  - ♦ short term tests have lower reliability than long-term tests
  - ♦ ICS: 1hr test w/ series of standard activities
    - ♦ loss of < 1g within error = dry
    - ♦ loss of 1-2g: may be due to weighing error, sweat, or vaginal d/c
- Urologic examination
  - skin: neurofibromas, café au lait spots
  - lower back: evidence of spinal dysraphism (skin dimples, hair tufts, fat deposits)
  - perineal skin integrity
  - pelvic exam: examine w/ full bladder to assess UI
    - degree of vaginal atrophy: loss of rugae, mucosal fragility, petechiae, erosions
    - urethral hypermobility
      - ♦ Q-tip test
        - ♦ lubricated Q-tip placed transurethrally into bladder and withdrawn to BN where resistance felt
        - ♦ angle at rest from horizontal, angle w/ straining from horizontal noted
        - ♦ hypermobility = resting or straining angle >30° from horizontal
          - N women may have a +ve test (Fantl 1986)
        - ♦ reproducible but has not been correlated w/ imaging techniques
        - ♦ **no absolute relationship between the degree of urethral motion and the severity of SUI Sx** (Cross 1997)
    - testing for SUI, prolapse: cystocele, rectocele, enterocele, uterus or vaginal cuff
      - ♦ Anterior: Bonney test (fingers), Marshall test (Allis clamp)
        - ♦ may be compressing urethra directly
      - ♦ Middle/apical
        - ♦ enterocele vs. high rectocele: peristalsis in the enterocele
        - ♦ palpation of the rectovaginal septum: combined DRE and vaginal exam
      - ♦ Posterior + perineal body: anterior wall supported w/ speculum, observe defects in rectovaginal septum
    - pelvic floor muscle strength/integrity
  - DRE
    - rectal mass
    - fecal impaction
    - sphincter tone and sensation
    - fascial defect in women w/ rectocele
    - prostate exam
- General neurologic examination
  - MSE: general appearance and behaviour, LOC, orientation, memory, speech, comprehension, gait, demeanor, facial asymmetry
  - motor examination: strength, atrophy
  - sensory examination
  - reflexes
    - DTRs
      - ♦ biceps: C5-6
      - ♦ triceps: C7
      - ♦ quadriceps: L3-4
      - ♦ ankle: L5-S2
    - cutaneous reflexes
      - ♦ **abdominal reflex**: lateral to medial scratching of the abdomen causes ipsilateral contraction
        - ♦ afferent/efferents: **segmental** sensory and motor nerves
        - ♦ above umbilicus **T8-T9**
        - ♦ below umbilicus **T10-T11**



## Chapter 27 Questions - UI.doc

- ♦ may be absent w/ obesity, prior abdo surgery, frequent pregnancy, pyramidal tract involvement above level or peripheral n. lesion
- ♦ **cremasteric reflex**: stroking inner thigh causes cremasteric contraction
  - ♦ tests **L1-L2**
  - ♦ sensory afferent: ilioinguinal/genitofemoral (L1/2) if the *anterior 1/3 scrotum* is stroked (NB: posterior 2/3 inner has S3 innervation off the posterior scrotal from the perineal n. and the perineal branch of the posterior femoral cutaneous n.)
  - ♦ motor efferent: genitofemoral → cremasteric muscle
- sacral reflexes
  - ♦ BCR: place finger in rectum, pull Foley or squeeze clitoris/glans → tests integrity of S2-4
- Uroflow
- PVR: < 50cc is normal, > 200cc is abnormal
- Urodynamics
  - "eyeball UDS"
    - insert Foley, get PVR
    - place Toomey syringe onto Foley, slowly pour in water
    - meniscus = estimate of Pves in cm H<sub>2</sub>O
  - single-channel
    - cannot differentiate b/w increase in Pabd vs. Pdet
  - multi-channel +/- video
    - VLPP is a good index of sphincteric function: gradually increase Pves via Valsalva until leakage seen
    - DLPP: measure by filling bladder and determining detrusor pressure at which there is leakage from the urethra (w/o increasing abdominal pressure, as in VLPP)
  - sphincter EMG
    - provides information regarding integrity of innervation to urethral sphincter and pelvic floor muscles
  - UPP
    - routine measurement not necessary or useful
  - ambulatory UDS
    - more physiologic
    - higher incidence of detrusor activity seen
- Cystoscopy

### What is the definition of hypermobility on the Qtip test?

- resting or straining angle of more than 30 degrees from the horizontal

### What are the indications for cysto in the pt w/ UI?

- persistent sx of urgency and frequency
- recurrent UTI
- hematuria
- voiding difficulties
- hx anti-UI surgery

### How does genital prolapse affect UI?

- affects urethra by pulling open the posterior urethral wall
  - may cause sphincteric incontinence
- obstructs urethra
  - causes BOO
  - may prevent voiding
  - may mask sphincteric incontinence
- dissipates effects of abdominal pressure on the urethra

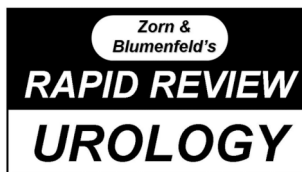
### What are the possible treatments for UI?

- Detrusor overactivity (UUI)
  - treat underlying condition: UTI, stone, foreign body, cancer
    - UTI most common cause
  - behaviour modification
  - medical therapy
    - anticholinergics
    - TCA
    - muscolotropic relaxants

## Chapter 27 Questions - UI.doc

- CIC
- electrical stimulation
- biofeedback
- neuromodulation
- surgical treatment
  - detrusor myomectomy
  - augment
  - TURP: relief of DI in > 2/3 of men
- Stress UI (SUI)
  - Nonsurgical
    - estrogens: high concentration of estrogen R in urethra
      - ◆ enhance  $\alpha$ -adrenergic R density and sensitivity
      - ◆ trophic effects on urethral mucosa, submucosa, and collagen
      - ◆ contraindicated in women w/ hx of breast cancer
        - ◆ increased risk of endometrial cancer if no progesterone
    - pelvic floor exercises
    - biofeedback
    - electric stimulation
    - neuromodulation
  - Surgical
    - injections
    - transvaginal suspensions
    - retropubic suspension
    - slings
    - AUS
- Mixed UI
  - if SUI sx predominate: surgery corrects in 50-70% pts
  - must proceed w/ noninvasive medical management prior to surgery





## Chapter 28

### • Post-prostatectomy Incontinence •

---

#### What is the incidence of UI after RRP?

- controversial: rates vary greatly
  - based on physician assessment: subjective leakage 5-10%, pad use 1-10%
  - based on pt questionnaires: subjective leakage 30-50%, pad use 5-20%
  - does not correlate w/ bother
- prevalence has likely increased due to increase in # of procedures performed annually

#### What is the cause of post-RP (or post-TURP) incontinence?

- Failure to store, due to the bladder:  $P_{det}$  overcomes resistance of BN/EUS
  - involuntary contractions
    - detrusor instability in 17-32% of men undergoing RP
    - detrusor instability in 53-80% of men w/ BPH
    - instability increases w/ age
  - decreased compliance
    - has been seen due to OR
- Failure to store, due to the outlet
  - direct injury to sphincter or supporting structures, neural innervation or pre-existing injury
    - resection in TURP distal to veru may **injure EUS**: usually anterior b/w 11 and 2 o'clock position
      - ◆ sphincteric injury is the main cause of UI post-RP
    - **damage to nerves**: nerve-sparing RP may preserve continence
    - **RP decreases urethral length** but no difference in MUCP
- Overflow incontinence
  - obstruction from residual adenoma, BN contracture (most common), or urethral stricture
    - slow stream initially, then retention

#### What is the relative incidence of bladder and sphincter dysfunction to post-prostatectomy UI?

- RP
  - 30-45% incidence of detrusor instability
    - sole cause of UI in 1-4%
  - 80-99% incidence of sphincteric dysfunction
    - sole cause of UI in 40-60%
- TURP / open prostatectomy
  - 60-75% incidence of detrusor instability
    - sole cause of UI in 7-77%
  - 20-90% incidence of sphincteric dysfunction
    - sole cause of UI in 20-50% → may be referral bias

#### What are the RF for UI after RP?

- advanced **age**
  - atrophy of the rhabdosphincter
- advanced **stage** of disease
  - may alter surgical technique
- **surgical technique**
  - nerve sparing may increase continence post-op
- **experience** of surgeon
- **pre-op continence** status
  - UI present in 0-20% of pts pre-op
- previous **radiation**

## Chapter 28 Questions - Post-RP UI.doc

- UI after salvage RP range from 57-64%
- TURP after brachy: UI rates up to 70%
- prior **TURP**: controversial

### How does surgical technique affect sphincteric function?

- TURP
  - aggressive TURP around apex and beyond veru → increased risk of sphincteric damage
- RP
  - nerve-sparing: higher rate of functional continence in nerve-sparing group (94% vs. 70%)
    - preservation of autonomic nerves in NVB may contribute to distal urethral sphincter function
    - may relate to more careful dissection around the sphincter
  - ligation of dorsal complex: may damage sphincter
  - preservation of puboprostatics
  - BN sparing and tubularization: controversial
    - no difference in continence rates at 1 year, but may improve time to achieving continence

### What are the most common times that nerves may be damaged during RP?

- during blunt dissection of posterior periurethral tissues w/ R angle
- during placement of 5 and 7 o'clock sutures
- dissection of SVs

### How does one evaluate pts w/ post-RP incontinence?

- refer to Chapter 25 + 27
- History
  - incontinence: type, severity, precipitating events, # of episodes per day, pad use, effect on QOL
  - LUTS
  - PMHx: neurologic disease/sx, prev pelvic/urologic procedures, rads, bowel habits
  - Sexual hx
  - Meds
- Physical
  - bladder palpation
  - DRE
  - Valsalva: examine for SUI
  - DTR, perineal sensation, sphincter tone, BCR
- Labs
  - BUN, Cr, U/A
- UDS
  - uroflow
  - PVR
  - CMG: contractions, compliance, capacity
  - VLPP
  - UPP: MUCP, functional urethral length → no cutoff, ++ overlap b/w normal and abnormal
  - video UDS
- Cysto
  - in select cases: r/o stricture, trabeculation, diverticulae
- Imaging
  - RUG, VCUG: only if needed
  - US abdo: if pyelo, increased Cr, significant bladder dysfunction

### What is the treatment of post-RP incontinence?

- refer to Chapter 26
- General
  - lifestyle changes
  - fluid restriction
  - behaviour modification
  - biofeedback
  - Kegels
    - does not affect development of total UI
    - may speed time to achieve continence and improve need for pads
- Bladder dysfunction

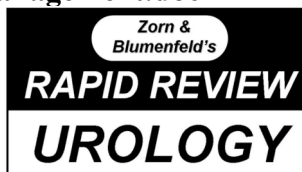
## Chapter 28 Questions - Post-RP UI.doc

- anticholinergics
- neuromodulation
- augmentation cystoplasty
- Sphincteric dysfunction
  - $\alpha$ -agonists, imipramine: minimal effect post-RP
  - urethral bulking agents: limited use due to scarring
    - success rates w/ GAX-collagen 36-69%, 4-20% dry
    - multiple injections needed
  - AUS
    - most effective long-term treatment for UI 2° to sphincteric dysfunction
    - limited to pts w/ severe bother and QOL
    - continence rates 80%, satisfaction in 90%
  - sling
    - increases VLPP: 56% cure, 8% improved
  - diversion: if rads, severe strictures

### What factors may negatively influence results after injection therapy for post-RP incontinence?

- extensive scarring or stricture
- previous rads
- high-grade SUI
- low ALPP





## Chapter 29

### • Urinary Incontinence: Nonsurgical Management •

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**Of UUI vs. SUI, which affects QOL more and why?**

- UUI - unpredictable

**What other factors associated w/ UI will decrease QOL?**

- depression
- loss of sleep
- sexual activity
- increased risk of falls
- forced institutionalization

**What are the basic nonsurgical therapies available to treat UI?**

- First line
  - Treatment of bladder
    - Behavioural therapy
      - ◆ **BEHAVE**: for both bladder and outlet
        - ♦ can cause significant reduction in # of incontinence episodes or amount of urine lost: 40-80%
      - ◆ Bladder retraining
        - ♦ timed voiding: start at longest consistently dry interval, increase by 15-30min/week
        - ♦ watch w/ timing alarm
        - ♦ review pts response to urge
        - ♦ **must always combine medical therapy w/ bladder retraining**
      - ◆ Education
        - ♦ what accounts for urine volume, what is normal
      - ◆ Habits: lifestyle changes and dietary modification
        - ♦ fluid limitation, avoid irritants
      - ◆ Asked/prompted voiding + scheduled toileting
        - ♦ for mentally challenged ppl
      - ◆ Voiding diary
      - ◆ Exercises: pelvic floor physiotherapy and rehabilitation
        - ♦ Basic: at home
          - Kegel exercises: quick flicks
          - Vaginal cones
          - Simple home perineometry
        - ♦ Advanced: require trained therapist/equipment
          - office-based EMG biofeedback
            - biofeedback = any technique that trains pts control via providing information about that fn
          - passive techniques
            - peripheral electrical stimulation (E-stim)
            - magnetic stimulation
    - Medical therapy: UUI
      - ♦ anticholinergic agents
      - ♦ drugs w/ mixed actions
      - ♦ CCB
      - ♦ K channel openers
      - ♦ PG inhibitors
      - ♦  $\beta$ -adrenergic agonists
      - ♦  $\alpha$ -adrenergic antagonists



## Chapter 29 Questions - UI medical management.doc

- ♦ TCAs, SNRIs
- ♦ DMSO
- ♦ polysynaptic inhibitors
- ♦ capsaicin, resinaferotoxin
- Treatment of outlet
  - Medical therapy
    - ♦  $\alpha$ -agonist monotherapy
    - ♦ ephedrine and pseudoephedrine
    - ♦ estrogen monotherapy (SUI in women)
    - ♦  $\alpha$ -agonist + estrogen
    - ♦ TCA/SSRI: imipramine
    - ♦  $\beta$ -antagonists: unmask/ $\uparrow$   $\alpha$ -tone
    - ♦  $\beta$ 2-agonists: striated muscle contraction
  - Devices for SUI
    - ♦ urethral meatal devices
    - ♦ urethral stents
  - Pessaries / vaginal support devices
- Second line
  - peripheral electrical stimulation
  - magnetic stimulation
  - sacral neuromodulation

### What are the different components of behavioural therapy for UI?

- **focus is education** - instruction about normal function of lower urinary tract and function
- urge inhibition
- timed voiding
- fluid/dietary management
- voiding diary
- pelvic muscle training: Kegel exercises

### What is the long-term efficacy of behavioural tx for UI?

- 85% initially and 50% 3-yr RR
- >50% RR in SUI and UUI

### How well do pts do PFEs/Kegels with simple instruction?

- 50% unable to perform proper contraction
- 25% promote incontinence with their efforts
  - Kegel routinely used a perineometer

### How do vaginal cones work for UI?

- cone inserted into vagina above levator
- biofeedback produced when pt feels cone slipping down
- levators used to prevent cone falling out

### What are the limitations of vaginal cones?

- many pts can't use any vaginal device
- many pts can't retain the lightest cone
- some pts retain cones w/ thigh adduction and not levator contraction

### What is the disadvantage to pressure-based biofeedback (perineometers) for UI?

- abdominal pressure is transmitted to the probe
  - pt may perform Valsalva (counterproductive) and believe pelvic muscles are contracting

### How can one classify E-stim for UI?

- high-frequency stimulation (50-100Hz)
  - directly stimulates contraction: mechanism of improvement not known
- low-frequency stimulation (5-20Hz)
  - activates inhibitory nerves to the bladder and reduce instability
    - vaginal electrodes
    - anal electrodes

## Chapter 29 Questions - UI medical management.doc

- posterior tibial electrodes: more acceptable for some men

### What is the mechanism of electromagnetic field therapy for pelvic floor rehab?

- Neotonus machine
  - treatment chair, emits electromagnetic waves to expected areas of pelvic floor muscles
  - 20 min session, includes high and low-frequency stimulation

### What are the advantages and disadvantages of magnetic therapy?

- Advantages:
  - no internal probe - increased pt acceptance
  - tech w/ minimal training needed
  - no supervision
- Disadvantage: must be administered in MDs office

### What is the efficacy of E-stim and magnetic tx?

- E-stim: decreases leakage episodes, decreases pad use, improves pelvic muscle strength
  - no evidence that electrostimulation is any different than other physical therapies
- Magnetic: 34% dry, decreased UI episodes
- No comparative studies available

### What pelvic floor rehab technique is the most efficacious in the treatment of UI?

- PFM exercises are effective in treating SUI
- No evidence that PFM + biofeedback is more effective than PFM alone
- No difference b/w electrostim vs. other physical therapies

### What class of medications have been used to treat SUI?

- alpha-adrenergics
- estrogens
  - most studies suggest superiority of E2 to placebo
  - one large scale RCT placebo-controlled study showed worsening UI - only 26% had pure SUI

### How well can medications for OAB be expected to work?

- eliminates UI in 20-30%, produces significant improvement in 50%

### How well do the various medications available for OAB compare?

- Appell: Detrol vs. Ditropan IR → no difference in efficacy, but tolerance better w/ Detrol
  - tolterodine 5 mg = oxybutynin 2 mg: ↓ incontinent episodes (50%), ↓ frequency (20%), ↑ voided volume
  - S/E: tolterodine < oxybutynin: ↓ dry mouth (freq and intensity), dose reductions and withdrawals
- ditropan XL vs. detrol (OBJECT trial – OAB: Judging Effective Control and Treatment)
  - 10mg ditropan XL vs. 2mg Detrol
- 2 RCTs compared Detrol vs. Ditropan s/e
  - Appell 2001: 12 week RCT double blind of overactive bladder oxybutynin XL vs. tolterodine IR
    - no significant difference in efficacy w/ similar incidence of S/E
  - Chapple 2001: small double blind randomized crossover in males to assess dry mouth using long-acting preparations – Detrol LA vs. Ditropan XL
    - efficacy Detrol LA 6 mg = Ditropan XL 20 mg, but ↓ dry mouth in Detrol arm
- oxybutynin IR > oxybutynin XL ≥ tolterodine IR ≥ tolterodine LA
  - NB: these are *extrapolations* since as of 2001 only 2 RCT (Appell 2001, Chapple 2001) comparing oxybutynin and tolterodine have been performed
- in general, tolterodine tested on anticholinergic-naïve pts whereas ditropan XL tested on pts who tolerate IR formulation

### What are the effects of imipramine on the GU tract?

- closure of BN and proximal urethra
- suppresses bladder overactivity

### What are the indications for urethral plugs and pessaries?

- inoperable patient
- periodic, situational and mild SUI (e.g. exercise)
- elderly women who cannot comply w/ behavioral therapy
- collagen injection contraindicated

## Chapter 29 Questions - UI medical management.doc

- younger pt awaiting surgery
  - generally reserved for females w/ SUI and should not be used in the NGB population
  - external penile compression devices should not be used in males w/ NGB b/c of potential tissue damage, esp. in the face of sensory impairment

### What are the advantages and disadvantages of using urethral devices for UI?

- Advantages
  - pts skeptical about results of OR
  - pts afraid of OR
  - medical tx for UI not adequate
  - UI pts already pay for pads, and will pay for devices
  - devices cost-effective
- Disadvantages
  - devices thought to be "last-resort"
  - pts skeptical of devices
  - difficult to reach target consumer
  - MD has no incentive to promote device
  - costs are prohibitive

### What 3 urethral meatal devices have been marketed for SUI?

- Capsure
- Femassist
- Impress
  - all 3 discontinued due to lack of interest

### What 3 urethral stents have been marketed for SUI?

- ContiCath
- Reliance
- FemSoft

### What are the stages of sacral nerve stimulation?

- initial PNE (peripheral nerve evaluation)
- surgical implantation of device

### Describe the technique for PNE.

- pt prone
- local anaesthesia
- sacral nerve foramina localized w/ needle based on bony landmarks
  - fluoroscopy
- S3 localization: flexion of ipsilateral great toe, flexion of anal muscles
  - pulling/fluttering sensation in vagina, prostate, or rectum
- place temporary wire through needle, wire secured
- wire worn x 1 week w/ external stimulator
- successful PNE: >50% reduction in sx
  - repeat if borderline sx

### What are the complications of PNE?

- lead migration
- temporary pain
- skin irritation
- adverse change in bowel/bladder function
- electrode fracture

### What are the contraindications for sacral neurostimulation?

- end-stage, small contracted bladder
- peripheral nerve injury/sacral spinal cord injury
- spinal cord tumour
- areflexic bladder from myogenic damage from chronic overdistension

### What important pieces of information can be obtained from a voiding diary?

## **Chapter 29 Questions - UI medical management.doc**

- largest voided volume: correlates w/ cystometric capacity
  - <150-200cc: more severe bladder dysfunction
  - >300cc: better potential bladder function
- voiding interval: can determine "safe" interval to begin bladder training
- baseline voiding function
- involves pt in treatment process

### **How can one score pelvic muscle strength by vaginal exam?**

- Laycock scale
  - 0-6: absent, flicker, weak, moderate, good, strong
- Romanzi scale: score of 9 (0-3 each)
  - pressure: none, weak, moderate, strong
  - duration: none, <1sec, 1-5sec, >5sec
  - displacement: none, slight anterior, whole anterior, gripped

### **How can pts be classified based on pelvic floor evaluation?**

- based on assessment of pelvic floor muscle strength at baseline
  - Group 1: no or minimal ability to isolate and contract levators
  - Group 2: isolate correct muscles, w/ poor strength
  - Group 3: good pelvic floor muscle strength and isolation

### **What is the initial treatment of UI based pelvic floor evaluation?**

- group 1: need biofeedback – cannot start w/ home exercises
  - weekly office sessions, convert later to home unit
  - E-stim or magnetic stim
- group 2: good candidates for pelvic muscle rehab
  - written instructions and follow-up visit w/ RN to determine progress
- group 3: value of pelvic floor rehab is unclear
  - instruct pt in "quick flicks"
  - offer vaginal cones

### **What are the 2 principal treatments for SUI?**

- pelvic floor rehabilitation
- surgery

### **How do the results of surgery and rehab compare?**

- surgery is the single most effective treatment
- 40-50% satisfied w/ response to rehab – may avoid OR

### **Which pts will benefit from immediate surgery for SUI?**

- significant associated prolapse (beyond hymenal ring)
- highly motivated to be completely dry
- high levels of physical stress due to lifestyle or occupation
- severe SUI

### **What are the indications and contraindications for medical therapy?**

- Indications
  - low max voided volume
  - underlying neurologic disease
  - uninterested or unable to participate in behavioural techniques
- Contraindications
  - very large bladder capacity
  - medical reasons to avoid anticholinergics
  - very old
  - very young

### **How does one manage the refractory OAB?**

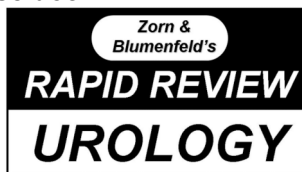
- Investigations
  - urodynamics
  - cystoscopy

## Chapter 29 Questions - UI medical management.doc

- Treatment
  - anticholinergic + imipramine
  - sacral neuromodulation
  - surgical reconstruction

### How does one manage mixed UI?

- Hx: determine which component (SUI or UUI) occurred 1<sup>st</sup>: often is primary problem
- Tx
  - pessary trial: elevation of cystocele will unmask occult sphincteric UI in > 50%
  - benefit from each form of conservative tx: behavioural, pelvic floor rehabilitation, and medical tx



## Chapter 30

### • Vaginal Reconstructive Surgery for Sphincteric Incontinence and Prolapse •

---

#### What is the prevalence of incontinence and prolapse?

- lack of conformity among studies: definition, survey methods, validation
  - US: 37%
  - Europe: 26%
  - UK: 29%
- steadily increasing prevalence w/ age
  - young adult: 20-30%
  - middle age: 30-40%
  - elderly: 30-50%
- in women w/ pelvic floor problems, prevalence of anal incontinence 28-29%
- lifetime risk of undergoing single OR for prolapse or UI by age 80: 11.1%
- 38% of women w/ UI have prolapse

#### What definitions of UI have been used for UI in incidence studies?

- any uncontrolled urine loss in past 12mo w/o regard to severity
- >2 incontinent episodes per month
- ICS definition: condition in which UI is a social or hygienic problem and is objectively demonstrable

#### What are the RF for SUI and pelvic organ prolapse?

Mnemonic - C-PROLAPS

- **Constipation:** repeated straining exacerbates dysfunction
- **Pregnancy** and childbirth
  - vaginal delivery is major RF for pelvic floor dysfunction
    - labour and delivery causes nerve damage, muscular damage, and direct tissue stretching and disruption
    - link b/w parity and UI
  - episiotomy: controversial role
- **Respiratory** problems and smoking: cough
- **Obesity:** wt loss improves sx
- **Lifting** and exercise
- **Aging:** age-related lower urinary tract changes
- **Prenatal** and congenital factors
  - connective tissue weakness: leads to anatomic defects
  - bladder extrophy: propensity for pelvic organ prolapse
  - DMD, myelodysplasia: pelvic muscle paralysis
- **Surgery:** prolapse requiring surgery higher in pts w/ TAH
- **menopause**
  - no difference b/w pre- and post-menopausal groups for UI
  - may have effect on prolapse

#### What muscular supports make up the pelvic floor?

- Pelvic diaphragm
  - levator ani
    - pubococcygeus (medial)
      - ◆ elevates rectum, vagina, and urethra anteriorly → passes horizontally behind rectum
      - ◆ aids in compression of lumens
      - ◆ connected to viscera via puborectalis, pubourethralis, pubovaginalis
    - iliococcygeus (lateral)
      - ◆ fuses w/ pubococcygeus to form **levator plate** → supports rectum and vagina
      - innervated by S3-4 via pudendal nerve

### Chapter 30 Questions - Vag OR + Prolapse.doc

- **arcus tendineus levator ani** runs from pubic ramus to ischial spine, along surface of obturator internus
- coccygeus
- levator plate: median raphe b/w anus and coccyx
  - formed by fusion of iliococcygeus and posterior fibers of pubococcygeus
- Urogenital diaphragm
  - separate musculofascial structure below pelvic diaphragm
  - may contain sheet of muscle extending across pubic arch or 3 contiguous muscles
    - compressor urethrae, sphincter urethrae, and urethrovaginalis
  - inferior fascial layer: perineal membrane
- Perineal body

### What are the connective tissue supports of the female pelvic floor?

- Anterior
  - connective tissue supports of the urethra, bladder, and vagina: extend to arcus tendineus pelvic fasciae on pelvic diaphragm
    - "hammock" of anterior vaginal wall tissue supports BN and urethra
  - pubourethral ligaments: extend from urethra to pubis
    - may be 2 separate structures: one at BN, one distally
  - anterior vaginal wall: supports urethra by lateral attachment to levators
  - urethropelvic ligaments from suburethral fascia at BN and proximal urethra to levators and arcus tendineus
    - separate from hammock
- Middle
  - cardinal ligaments (aka transverse cervical ligaments of Mackenrodt)
    - extend from lateral cervix and upper vagina to lateral pelvic walls
  - uterosacral ligaments
    - attached to cervix and upper vaginal fornices posterolaterally
    - hold uterus and vagina over levator
- Posterior
  - posterior vaginal wall supported by paracolpium
  - rectovaginal fascia
  - lateral rectal ligaments: fascial supports for rectum
    - extend from posterolateral pelvic sidewall to rectum
    - surround middle rectal arteries

### How can one classify the different types of pelvic organ prolapse?

- Anterior vaginal wall (Anterior compartment)
  - Cystocele
    - central, lateral, combined
  - Urethrocele: rare
- Apical vaginal wall (Middle compartment)
  - Enterocoele: anterior type, posterior type → lateral less common
    - in relation to uterus: through vesicouterine or rectouterine (more common) space
    - peritoneum lined sacs containing small bowel or omentum
  - Uterine prolapse
    - can vary from minimal to total procidentia
  - Uterovaginal: w/ cystocele, enterocoele, rectocele
  - Vaginal vault eversion (post TAH): w/ cystocele, enterocoele, rectocele
- Posterior vaginal wall (Posterior compartment)
  - Rectocele: high, low, midvaginal
- Perineal body defects

### What are the different types of enteroceles?

- congenital
  - in cul-de-sac, due to failure of fusion or reopening of fused peritoneal leaves down to perineal body
- post-TAH vault enteroceles
  - may be due to increased IAP
- enterocoele associated w/ cystocele and rectocele
  - from traction by prolapsing organs
- iatrogenic
  - due to surgical procedure that changes vaginal axis

## Chapter 30 Questions - Vag OR + Prolapse.doc

### How does one evaluate the pt w/ pelvic organ prolapse?

- History
  - Urinary sx: SUI, UII, LUTS
  - Bowel sx: anal incontinence, constipation, difficult defecation, tenesmus
  - Sexual sx: dyspareunia, decreased libido
  - Other local sx: vaginal pressure/heaviness, vaginal or perineal pain, sensation of tissue protruding, LBP, abdo pain, mass
    - need to manually reduce prolapse to void, unusual position to void, retention
  - Questionnaires
    - UDI-6: Presence of → frequency, urgency, SUI, small amounts of leakage, difficulty voiding, pain
    - IIQ-7: UI affecting → IADLs, physical activity, entertainment, travel, social life, emotional health, frustration
    - SEAPI QMM system: SUI, Emptying, Anatomy, Pads, Inhibition, QOL, Mobility, Mental status → each from 0-3
  - Voiding diary
- Physical
  - abdo exam: incisions, hernias, masses, bladder
  - neurourologic exam: MSE, mobility, focused neurologic exam if needed
  - pelvic exam: dorsal lithotomy, semi-upright, upright, w/ full and empty bladder
    - external genitalia: estrogen deficiency, discharge, prolapse, masses
    - bimanual exam
    - urethral hypermobility: Q-tip test
      - ◆ +ve test = maximum strain axis of > 30 degrees from horizontal
    - Marshall/Bonney test: anterior vaginal wall → cystocele
      - ◆ produce continence by restoring anterior vaginal wall hammock
    - posterior wall → rectocele
    - cervix, uterus, vault → apical wall
    - rectovaginal septum
    - perineal body: may be thinned or expanded
    - anal sphincter
    - levator ani assessment
      - ◆ palpate in posterior vagina 2-4cm above the hymen
- Pad test
  - ICS standard: give Pyridium and check pad after 1h of physical activity
    - +ve test: orange stain and weight gain of >1g
- Labs
  - U/A
- UDS
  - PVR
- Cysto: if necessary
- Imaging
  - US
  - MRI: may be helpful w/ complex prolapse

### What is "occult or potential SUI"?

- production of SUI by reduction of vaginal prolapse
- present in up to 80% pts w/ severe SUI
- due to kinking of urethra by cystocele or external urethral compression

### How can one classify female sexual dysfunction?

- Sexual desire disorders: hypoactive sexual desire, sexual aversion
- Sexual arousal disorders
- Sexual pain disorders: dyspareunia, vaginismus, other
- Orgasmic disorders

### What are the indications for evaluation of POP beyond the basic clinical eval in UI?

- uncertain diagnosis
- inability to develop treatment plan based on basic diagnostic evaluation
- lack of correlation b/w sx and findings
- failure to respond to pt satisfaction



### Chapter 30 Questions - Vag OR + Prolapse.doc

- consideration of surgical intervention
- hematuria w/o infection
- other comorbid conditions: UI + UTI, previous surgery
- severe prolapse
- abnormal PVR
- neurologic disease: MS, SCI

#### What are the indications for cysto in the evaluation of UI?

- sterile hematuria/pyuria
- recent onset irritative sx w/o reversible causes
- bladder pain
- recurrent UTI
- suspected intravesical FB
- failure of UDS to reproduce sx

#### How can one classify severity of pelvic organ prolapse?

- Severity (Porges)
  - 1<sup>st</sup> degree (slight): cervix inside introitus w/ straining
  - 2<sup>nd</sup> degree (moderate): cervix outside introitus w/ straining
  - 3<sup>rd</sup> degree (marked): cervix outside introitus w/ rest
- Vaginal profile (Baden)
  - Grade 1: cervix < ½ way to midplane of vagina
  - Grade 2: cervix > ½ way to midplane of vagina, inside hymenal ring
  - Grade 3: cervix outside of hymenal ring
  - Grade 4: complete eversion
- Beecham
  - 1<sup>st</sup> degree: cervix inside introitus
  - 2<sup>nd</sup> degree: cervix outside introitus
  - 3<sup>rd</sup> degree: complete eversion
- ICS POPQ (Pelvic organ prolapse quantification)
  - site-specific quantitative description of support that locates 6 defined points around the vagina w/ relation to hymen
    - 3 anterior: Aa (3cm proximal to hymen anteriorly), Ba (lowest pt of prolapse b/w Aa and apex), C (cervix)
    - 3 posterior: Ap (3cm proximal to hymen posteriorly), Bp (lowest pt of prolapse b/w Ap and apex), D (pouch of Douglas)
      - ◆ after TAH, D is omitted and pt C is vaginal cuff
    - also measure vaginal length at rest (tvL), genital hiatus (gh) from meatus to posterior hymen, and perineal body (pb) from posterior gh to midanal opening
  - gives -ve #s (in cm) to structures that have not prolapsed beyond hymen, +ve #s to structures that protrude, plane of hymen defined as 0
    - Stage 0: no prolapse seen
    - Stage I: most distal portion of prolapse > 1cm above hymen
    - Stage II: most distal portion of prolapse is within 1cm (proximal or distal) of hymen
    - Stage III: most distal portion of prolapse protrudes > 1cm below hymen, but is < 2cm less than total vaginal length (not all vagina is prolapsed)
    - Stage IV: complete eversion

#### What are the results of vaginal surgery for SUI?

- early reports w/ short-term follow-up showed success rates comparable to retropubic suspensions
- long-term follow-up lower
  - 4 yr cure rate 67% (vs. 84% suspensions, 83% slings)
- good option for pt w/ SUI, smaller volume UI, less ISD, and are willing to accept worse long-term F/U for lower immediate morbidity

#### What is the pre- and post-op management for vaginal suspensions?

- dorsal lithotomy w/ Trendelenberg
- weighted vaginal speculum
- Foley
- injection of NS into mucosa for vaginal incision
- cysto to check suture placement
- vaginal packing: depending on bleeding

**What are the various techniques of performing vaginal suspension for SUI?**

- Pereyra +/- modification
  - original Pereyra: T-shaped vaginal incision w/ minimal periurethral dissection, no penetration into retropubic space
    - needle delivered into vagina through single midline incision
    - single needle stylet and absorbable suture fix periurethral tissue over rectus fascia
  - modified Pereyra: incorporates BN plication w/ absorbable suture
- Stamey needle BN suspension
  - endoscopy to ensure sutures placed at BN
  - nonabsorbable suture w/ Dacron pledgets to buttress each side of urethra and prevent pull-through
  - single-pronged blunt-tipped needle (Stamey needle) used
  - 2 lateral SP incisions
  - 70-90% success, erosion of pledgets up to 3yrs post-op
- Gittes BN suspension
  - 2 lateral SP stab incisions made, Stamey needle passed 2X on each side from over rectus fascia through vaginal wall
  - guided by Foley balloon to be at BN
  - #2 Prolene used
  - Mayo needle used to take helical bites of vaginal tissue
  - sutures tied loosely over rectus fascia, sutures form "autologous pledget"
  - worst long-term outcome: 37% at 6yrs
- Raz procedure
  - modification of Pereyra: inverted-U vaginal incision
  - open retropubic space sharply by detaching periurethral connective tissue from arcus tendineus
  - blind passage of ligature carrier from abdomen to vaginal incision via finger guidance
  - poor long-term results: 14% dry at 4yrs
- Raz vaginal wall sling
  - rectangular flap of vagina buried at BN, suspended by nonabsorbable sutures by passage of ligature carrier
  - modification eliminates buried flap:
    - 2 oblique incisions made in anterior vaginal wall from midurethra to 3cm beyond BN
    - dissect to enter retropubic space
    - proximal BN sutures placed w/ #1 Prolene w/ several bites of periurethral tissue
    - distal midurethral sutures placed w/ #1 Prolene
  - Raz vs. PVS: clinical success 94%, cured 75% in PVS vs. 80% success, 60% cured w/ Raz
    - vaginal wall slings recovered faster
- TVT
  - rejection rate of 10% w/ Gore-Tex and Mersilene tapes
  - 60-80cc anaesthetic injected into abdo skin above pubis, down along back of pubis into space of Retzius
  - anaesthetic injected into vagina in periurethral area
  - 2 abdo skin incisions of 1cm made, above pubis, 5cm apart
  - midline vaginal incision 1.5cm long, 1cm from meatus
  - 2 small periurethral spaces made, not entering retropubic space
  - catheter guide pushes bladder away
  - tip of needle brought from vagina to abdo incision
  - cysto
  - 91% cure rate in 1 yr followup
- Bone anchoring techniques
  - **no evidence to show they are superior to traditional needle suspensions in the long term**
  - In-Tac
    - bone anchors threaded w/ #1 Prolene inserted transvaginally w/ spring-loaded multiuse inserter
    - 1yr cure rate 82%
  - Vesica
    - drill to place screws into pubis through SP incision
    - #1 Prolene preloaded into screws, passed w/ suture passer into vaginal incision to suspend BN

**What are the results after needle suspensions?**

- poor long term results
  - not recommended as primary procedure

**What are the complications of vaginal suspension?**

- Intraoperative

## Chapter 30 Questions - Vag OR + Prolapse.doc

- bleeding
  - Tx: vaginal packing, suture ligatures
  - transfusion rates 1%
- suture passage through bladder
  - if hematuria seen, bladder puncture likely
- laceration of bladder or urethra
- ureteral injury
- peritoneal and bowel injury → fistula
- Postoperative
  - Early
    - voiding dysfunction and urinary retention: in 5-8% beyond 2 weeks
      - ◆ de novo intability or worsening of pre-existing instability, urgency, UUI: 4-16%
    - infection, abscess
  - Late
    - persistent pelvic pain or dyspareunia: 5%
      - ◆ may be due to entrapment of genital branches of GF or ilioinguinal nerve
    - suture erosion, stone formation
    - sling erosion
    - sling infection
    - osteitis pubis: noninfectious inflammation of the periosteum overlying the pubis
    - chronic voiding dysfunction
      - ◆ obstruction and incomplete emptying: wait > 3mo before doing anything
      - ◆ chronic irritative sx and UUI → must r/o obstruction
    - recurrent SUI
    - pelvic prolapse, enterocele, rectocele, cystocele: 6%
    - death: 0.05%

### What are the definitions of the following procedures:

- Colporrhaphy: repair of vaginal wall
- Colpocleisis: obliteration of vaginal lumen
  - LeFort: denudation of anterior and posterior vaginal mucosal strips w/ approximation of walls
- Colpectomy: resection of vagina
- Colpopexy: suspension of vaginal wall
- Culdotomy: incision into (posterior) vaginal wall (pouch of Douglas)
- Culdoplasty (culdeplasty): surgical obliteration of cul-de-sac to treat or prevent enterocele
  - Abdominal
    - Moschowitz: multiple purse-strings in uterosacrals laterally, posterior vaginal wall, and rectal serosa
    - Halban: 3-4 parallel sagittal sutures starting on posterior vaginal wall picking up peritoneum and rectal serosa
  - Vaginal: McCall → transverse suture in cardinals, uterosacrals, pararectal fascia, peritoneum, and posterior vaginal wall
- Perineorrhaphy: repair of perineal body

### What are the goals of surgery for pelvic organ prolapse?

- relief of sx
- maintenance or improvement of urinary, bowel, and sexual function
- repositioning of pelvic structures and supports to normal anatomy
- prevention of new pelvic support defects and sx
- correction of concomitant intrapelvic disease
- durable result

### What is important in the preop preparation for women undergoing vaginal surgery for prolapse?

- estrogen therapy
  - improves vascularity: 6 week course of vaginal estrogen cream

### What are the nonsurgical treatments for prolapse?

- improve chronic cough, obesity, constipation
- vaginal estrogen
- pessaries
- Kegels

## Chapter 30 Questions - Vag OR + Prolapse.doc

### What are the recurrence rates of prolapse after the various anterior vaginal repairs?

- Anterior repair: 0-20%
- Abdominal repairs
  - paravaginal defect, central defect: 5-8%
- Vaginal paravaginal repair: 7-32%
- 4-6 corner suspensions: 0-60%
- Anterior repair w/ needle suspension: 4-50%
- Anterior repair w/ sling: 0-17%
- Anterior repair w/ sacrospinous ligament fixation: 20-90%

### How can one classify vaginal surgical procedures for prolapse?

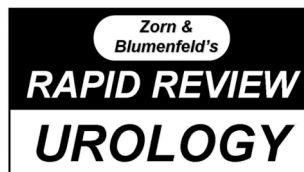
- Anterior vaginal wall (anterior compartment)
  - Anterior repair (colporrhaphy for central defect)
    - failure rate of 50% for UI → *not recommended for procedure for SUI*
      - ◆ incorporated into other transvaginal repairs done for UI
    - midline incision through vagina to 1cm below meatus, flaps dissected out
    - plication sutures of 2-0 or 3-0 delayed absorbable
    - Kelly procedure: sutures placed at level of urethra and BN by taking lateral tissue and approximating in midline
    - excess vaginal tissue trimmed, mucosa approximated
  - Procedures for lateral and combined defects
    - Abdominal repairs
      - ◆ paravaginal repair: **endopelvic fascia and lateral vaginal sulcus sutured to arcus tendineus**
      - ◆ Burch: distal **vaginal sutures inserted into Cooper's** ligament
      - ◆ low recurrence rate: 5-8%
    - Vaginal paravaginal repair
      - ◆ midline/inverted U vaginal incision, retropubic space entered
      - ◆ pubocervical fascia separated from sidewall of pelvis, exposing obturator fascia and arcus tendineus
      - ◆ 4-6 interrupted **sutures b/w arcus tendineus and pubocervical fascia**
    - Six-corner suspension
      - ◆ 2 incisions from midurethra to proximal vagina, enter retropubic space
      - ◆ attachments of bladder base exposed proximally to cardinal ligaments
      - ◆ proximal suture b/w cardinal ligament and vaginal wall, middle at BN, distal at midurethra
  - Anterior repair w/ suspension
    - w/ needle BN suspension
      - ◆ goalpost incision w/ distal limbs at midurethra, ending 1cm proximal to BN, midline to vaginal cuff
      - ◆ mucosa cleared laterally from fascial elements, enter retropubic space
      - ◆ repair enterocele if present
      - ◆ 0 Prolene used in 4 sutures proximally and distally, transferred to above rectus fascia w/ suture carrier
      - ◆ central defect fixed w/ colporrhaphy w/ interrupted 2-0 absorbable + mesh
    - w/ sling
      - ◆ midline vaginal incision from midurethra proximally to vaginal cuff/apex, flaps developed, retropubic space entered
      - ◆ anterior repair performed by plicating fascia
      - ◆ sling sutures passed to above rectus fascia, vaginal mucosa reapproximated above sling
- Apical vaginal wall (middle compartment)
  - Enterocele repairs
    - vaginal approach
      - ◆ lithotomy, Trendelenberg, rectal packing
      - ◆ vaginal apex grasped w/ Allis clamp bilaterally, incision made in vaginal wall
      - ◆ peritoneal sac dissected free from vaginal wall, opened, purse-string to exclude sac
      - ◆ excise peritoneum and excess vaginal wall, close mucosa
    - abdominal approach
      - ◆ approximate uterosacral ligament if TAH, obliterate cul-de-sac w/ circumferential sutures
  - Vault prolapse repairs
    - sacrospinous ligament fixation
      - ◆ longitudinal incision in vaginal mucosa over enterocele to posterior wall, vaginal wall dissected from sac
      - ◆ mobilize and close sac w/ high purse-strings and excise excess
      - ◆ palpate ischial spine and sacrospinous ligament
      - ◆ 2 #1 delayed absorbable sutures placed 1.5-3cm medial to ischial spine through ligament and tied to vaginal apex

### Chapter 30 Questions - Vag OR + Prolapse.doc

- uterosacral ligament suspension
  - ◆ midline vaginal incision, enterocele sac entered, bowel packed away
  - ◆ uterosacral remnants identified medial and posterior to ischial spines at 4 and 8 o'clock
  - ◆ 2-3 Prolenes placed bilaterally in USL, used to secure vagina
- iliococcygeus suspension
  - ◆ bilateral fixation of vaginal apex to iliococcygeus
  - ◆ success rates of 80-95%, may get vaginal shortening
- abdominal sacral colpopexy
  - ◆ indicated after failed vaginal repair, when concomitant abdominal OR required, or if unfamiliar w/ vaginal approach
  - ◆ low lithotomy, bladder drained, midline or Pfannenstiel to enter peritoneum
  - ◆ bladder and rectum dissected from vagina
  - ◆ 0 Prolene placed from one lateral fornix through 3cm wide Marlex mesh to other fornix
  - ◆ proximal end of mesh attached to sacral promontory
- colpocleisis
  - ◆ suture walls together after excising anterior and posterior vaginal strips
  - ◆ leave lateral channels for secretions
- Posterior vaginal wall (posterior compartment)
  - Posterior repair and perineorrhaphy
    - lithotomy, sponge in rectum, Foley
    - transverse incision to excise skin b/w 2 Allis clamps, excise triangular flap of mucosa
    - hug mucosa to avoid rectal injury
    - displace rectum posteriorly, running locked 2-0 absorbable suture incorporating full-thickness mucosa, rectovaginal fascia, and pararectal fascia
    - V-shaped incision b/w Allis clamps w/ apex towards rectum
    - perineal body reconstituted by placing interrupted U-shaped stitches to approximate the superficial and deep perineal muscles toward the midline
  - Rectovaginal fascia defect repair
    - vaginal mucosa dissected laterally through posterior midline incision
    - intact fascial edges sutured together
    - perineal muscles brought together
    - levators not plicated

#### What are the goals of posterior repair?

- plicate the prerectal and pararectal fascia in the midline
- narrow the posterior aspect of the levator hiatus w/ levator plication
- repair the perineal body



## Chapter 31

### • **Retropubic Suspension Surgery for Female Incontinence** •

#### What are the indications for retropubic repair?

- depends on whether anatomic SUI (genuine SUI – due to hypermobility of BN) or IDS or both exist
- failed conservative management plus:
  - presence of urethral hypermobility
    - vaginal and retropubic procedures have similar success rates: surgeon preference
  - pt requiring abdominal surgery that cannot be performed vaginally
    - ex: TAH, enterocele repair, vaginal cuff suspension by sacral colpopexy
  - limited vaginal capacity and mobility
- **if true type III SUI (ISD) exists, retropubic suspension procedure contraindicated**
  - no hypermobility exists → pt needs sling, injection therapy, or AUS

#### General Technical Issues (Webster Campbell's 2002)

|                              |  |
|------------------------------|--|
| <b>Retropubic dissection</b> | <ul style="list-style-type: none"> <li>- position: supine w/ legs abducted – low or modified dorsal lithotomy</li> <li>- Foley</li> <li>- Pfannenstiel or lower abdominal midline</li> <li>- all old adhesion should be taken down – preferably sharply</li> <li>- if evidence of obstruction, consider urethrolysis</li> </ul>  |
| <b>Suture material</b>       | <ul style="list-style-type: none"> <li>- <b>completely personal preference</b></li> <li>- original descriptions of MMK and Burch were w/ catgut</li> <li>- thought that scarring allows for continued fixation of the pervaginal tissues to the suspension sites; NAS may ↓ risk of suture dissolution before development of adequate scar (Raz 1996), but a nonrandomized, retrospective study absorbable vs. nonabsorbable showed no difference (Park 1988)</li> </ul> |
| <b>Tension</b>               | <ul style="list-style-type: none"> <li>- impaired detrusor contractility: beware of putting Pt into retention w/ excessive tightening</li> <li>- low DLPP: ensure adequate tension placed on Burch sutures or sling</li> </ul>   |
| <b>Bladder Drainage</b>      | <ul style="list-style-type: none"> <li>- urethral or SPC based on surgeon preference               <ul style="list-style-type: none"> <li>- SPC may have ↓ bacteriuria, UTI and return of bladder function (Andersen 1985, Bergman 1985) more comfortable</li> </ul> </li> <li>- TOV POD#1-5</li> </ul>  |
| <b>Drains</b>                | <ul style="list-style-type: none"> <li>- if concern about hemostasis</li> </ul>  |

#### What retropubic suspension procedures are available for SUI in women?

- Marshall-Marchetti-Krantz (MMK): anchor BN and proximal urethra to pubis
  - Pre-op
    - supine, low or dorsal lithotomy
    - Foley
  - Procedure
    - Pfannenstiel or lower midline abdominal incision
    - develop retropubic space bluntly
    - Marshall (1949): 3 pairs of sutures (double bites of tissue) w/ chromic through full-thickness vagina and urethra (excluding mucosa) into cartilaginous portion of pubis → **may cause osteitis pubis**
      - ◆ most proximal sutures at BN, may need to place through rectus sheath
    - Marchetti (1949): omitted urethral bite to prevent urethral injury
    - JP drain
  - Post-op
    - immediate post-op voiding difficulties expected: voiding trial at day 1-5
    - SP catheter may be favourable

## Chapter 31 Questions - MMK+Burch.doc

- Burch: anchor vaginal wall to Cooper's ligament
  - original procedure attached paravaginal fascia to arcus tendineus fascia pelvis
  - later changed to ileopectineal ligaments (Cooper's ligaments)
  - can only use if pt has enough vaginal mobility and capacity to allow lateral vaginal fornices to be elevated towards Cooper's ligament
    - 2-4 sutures placed bilaterally, most distally at BN, proximally 2cm lateral to this
    - do not tie sutures tightly: free suture material seen
  - Ball-Burch modification
    - *used in pts w/ ISD*: MUCP < 20 cm H<sub>2</sub>O
    - before perform Cooper ligament suspension, 2-3 sutures used to plicate the anterior urethral wall at proximal and mid urethra
    - 5yr cure rate 84%
- Paravaginal fascial repair [a.k.a. vagino-obturator shelf (VOS) repair]: anchor pubocervical fascia to arcus tendineus fascia pelvis
  - vaginal wall in area of BN identified, and 3 interrupted #1 Vicryl sutures placed at 1cm intervals through paravaginal fascia and vaginal wall (excluding mucosa) starting at BN, continuing 3cm proximal
  - passed through adjacent obturator fascia and underlying muscle at arcus tendineus fascia
  - Richardson (1981): more extensive attachment w/ 6-8 sutures
  - Turner-Warwick (1986): VOS repair incorporates only lower 4cm of vagina
  - should allow 3 fingers b/w pubis and urethra, preventing rotational descent
  - Vicryl or PDS used in original VOS
- Laparoscopic retropubic suspension
  - similar short-term compared to open
  - 30-50% success at 4 years (McDougall 1999, retrospective)
  - w/ longer follow-up, lap retropubic suspensions appear to fail
    - lap Burch not durable
  - **bottom line: early results comparable to open MMK or Burch, but poor durability of laparoscopic technique**

### What are the outcomes after retropubic suspension procedures?

- MMK
  - subjective continence in 88% by 1-6 yrs
  - longer follow-up: success rates decrease to 40% by 17yrs
  - mean duration of continence 79mo
- Burch
  - short- and medium-term outcomes good: 85-90% cure w/ 1-5 yrs
  - more durable than MMK w/ longer follow-up
  - cure/improvement in 70% at 14yrs
- paravaginal repair/VOS
  - paravaginal: cure > 90%
  - VOS: cure 60-85%

### What is post-colposuspension syndrome?

- pain in one or both groins at the site of suspension
- present in up to 12% of pts after Burch

### What are the complications of retropubic repairs?

- Intra-op
  - bleeding: 5% transfusion rate
    - transvaginal procedures: bleeding occurs at 2 points
      - ◆ dissection of vaginal wall off periurethral fascia, esp. if deep; stay above the glistening white surface of the fascia
      - ◆ perforation of the endopelvic fascia: best managed by transferring the suspension sutures/sling to the suprapubic region quickly + vaginal pack
    - management
      - ◆ suture ligation 1st maneuver f/b packing
      - ◆ approximation of anterior bladder to retropubic space
      - ◆ Foley balloon on traction may control (Kastske Urol Urotech 1987)
  - bladder/urethral injury: 2 layer repair, drain, Foley
  - ureteral injury: rare → stent vs. reimplant if severe
  - injury to adjacent organs

## Chapter 31 Questions - MMK+Burch.doc

- GU: urethra, bladder, ureter
- nonGU: peritoneal w/ bowel injury
- Post-op
  - general surgical complications: DVT, wound dehiscence, etc.
  - infectious
    - UTI
    - pelvic abscess
    - wound
  - voiding dysfunction
    - retention
      - ◆ immediately postop: 30-40%
      - ◆ etiology
        - ♦ **technical: #1 cause for prolonged postop retention**
          - due to overcorrection of urethral axis, from inappropriate suture placement or overly tightened
        - ♦ **edema: #1 cause for immediate postop retention**
        - ♦ preexisting detrusor dysfunction
        - ♦ denervation from extensive perivesical dissection
      - ◆ release of urethra resolves voiding sx in up to 90%
      - ◆ risk of retention for > 1month: <5% for all suspensions, risk permanent retention <5%
    - bladder hyperactivity
      - ◆ pre-op urgency increases risk of post-op urgency
      - ◆ risk: 66% if urge and instability present pre-op, 36% if urgency but no instability, 11% if neither pre-op
      - ◆ tx: anticholinergics, behavioural modification, neuromodulation, augment, myectomy
      - ◆ may need release if due to obstruction
  - recurrent SUI
  - vaginal prolapse exacerbation
    - present in 3-17%
    - Burch procedure elevates lateral vagina, worsening posterior vaginal wall weakness → enterocele
    - may need to obliterate pouch of Douglas if perform retropubic suspension
  - osteitis pubis
    - present in 1-3% after MMK
    - present 1-8 weeks postop w/ acute pubic pain radiating to inner thighs, worse w/ moving
    - tender over pubis
    - increased WBC, ESR
    - Xray: haziness to borders of symphysis and lytic changes
    - tx: bed rest, analgesics, +/- steroids
  - suture erosion: can be cut endoscopically
  - sling erosion/infection: consider removal of sling
  - fistula
  - nerve entrapment w/ pain

### How can one identify pts at risk for post-op voiding difficulties?

- hx of prior voiding dysfunction
- hx of urinary retention
- UDS features
  - large capacity bladders
  - increased compliance
  - poor sensation

### What is the management of post-op voiding dysfunction for UI surgery?

- Investigations
  - definition of obstruction difficult in women; most simply relax the pelvic floor to void, therefore any elevation in outlet resistance can cause a “relative obstruction” → significant voiding dysfunction
  - therefore, UDS often do not exhibit classic obstructive findings, however, finding of new onset postop Sx and finding of a retropubically angulated and fixed urethra on video generally indicate that obstruction exists (Carr 1997)
- Management
  - r/o UTI, involuntary contractions, foreign body reaction
  - CIC or Foley; permanent CIC an option in pts w/ severe incontinence preop



### Chapter 31 Questions - MMK+Burch.doc

- wait at least 3 months before intervention – most resolve by 4/52; unlikely to return to N voiding if persistent to 6 months
- UDS for persistent UR
- release the repair
  - cut suspension sutures from above for ‘overcorrection’: usu. one or both sutures
  - cut sling in midline thru vaginal incision
- urethrolisis may be the most effective overall technique: pressure-flow studies: unfortunately, can not be used in isolation since no correlation between UDS findings and the likelihood of successful voiding after urethrolisis (Nitti JU 1994, Foster JU 1993, Webster JU 1990); combination of videourodynamics helpful

#### How do the following procedures compare in terms of results:

- Retropubic repair vs. Needle suspension + anterior repair
  - retropubic suspensions (85%) more effective than either needle suspensions or anterior repairs (50-70%)
- Retropubic repair vs. PVS
  - no difference b/w retropubic suspensions (usually Burch) and PVS
  - PVS usually reserved for pts w/ multiple prior failed procedures, and ISD used as contraindication to retropubic suspension
  - **more post-op voiding difficulty w/ sling**
  - more vaginal prolapse w/ Burch
- MMK vs. Burch vs. Paravaginal repair
  - similar results b/w MMK and Burch: 89% and 84% overall cure
  - more cure w/ Burch vs paravaginal repair: sparse literature
- TVT vs. Burch (BMJ 2002 Ward)
  - honest study using the very strictest outcome measures: WHO, SF-36, ICI pad test
  - criticisms
    - what does the power of the study refer to?
    - should have blinded statistician, evaluator, etc.
    - method of TVT standardized whereas that of Burch essentially left up to surgeon
  - results
    - pts who withdrew from Burch group had less severe UI compared w/ average → potentially had –ve impact on Burch group
    - length of catheterization: protocol favors TVT group since removal mandated if no complications; in Burch group, decision to leave catheter arbitrary – longer than N
      - ◆ LS: TOV once pt mobilizing well
      - ◆ i.e. don’t put much wt on length in this study
  - complications
    - definition of hematoma: probably clinically driven by ↓ Hgb or other vs. imaging driven



**Chapter 32**  
• **Pubovaginal Slings** •

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**What is the difference b/w Type III SUI and ISD?**

- Type III SUI = SUI associated w/ little or no urethral mobility, but an **open nonfunctional proximal urethra**
  - by video UDS: open BN and proximal urethra at rest, or by a urethra that leaks at low  $P_{abd}$
- ISD = **low-pressure urethra**, characterized by low MUCP ( $<20\text{cm H}_2\text{O}$ )

**What are the indications for slings?**

- female SUI: **Type III SUI or ISD**
  - SUI associated w/ a low-pressure urethra, defined by UPP or VLPP
  - SUI associated w/ urethral diverticulum
  - SUI after repair of urethral diverticulum
- **neurogenic conditions**
  - myelodysplasia associated w/ total lack of proximal urethral function
  - APR, TAH, pelvic #, SCI at T12-L1
- men w/ UI associated w/ **RP**
- **tissue loss** or urethral erosion associated w/ total urethral failure
  - after long period w/ Foley, surgical misadventures, chemo/rads
  - urethral reconstruction w/ Martius flaps

**What are the alternative treatments for ISD other than PVS?**

- urethral bulking agents
  - improvement in mucosal coaptation
  - fat, muscle, chondrocytes, Teflon, Macroplastique, Durasphere, GAX-collagen
  - best results in pts w/ ISD and little hypermobility
  - cure/improvement in 70-90% at 2-3 yrs, may require multiple/repeat injections
- AUS
  - must perform video UDS, identify instability or decreased compliance

**What are the indications for AUS in women?**

- neurogenic bladder dysfunction w/ low ALPP
- severe "pipe-stem" ISD after multiple prior ORs
- loss of urethral function due to congenital anomalies or trauma

**What is involved in the pre-op evaluation of the pt undergoing PVS?**

- pelvic examination: bimanual, Q-tip test, Marshall/Bonney test, posterior wall, rectovaginal septum, sphincter, perineal body
- UDS

**What are the causes of low-compliance bladders?**

- radiation
- chemo
- prolonged catheter drainage
- obstructive uropathy
- bladder decentralization syndromes: radical pelvic surgery

**How can one determine the VLPP?**

- varies w/ position, catheter size, bladder volume, and effort
- 3-lumen 10F catheter used, pt upright on fluoro table, bladder filled to 200-300cc
- vaginal prolapse interferes w/ LPP, as abdominal pressure is dissipated in the prolapse

## Chapter 32 Questions - PVS.doc

- makes urethra appear better than it is

### Describe the technique of pubovaginal sling.

- Preop
  - single dose antibiotic
  - dorsal lithotomy
  - 16F Foley, clamped w/ Kelly
  - vaginal exam
- Procedure
  - Abdominal approach
    - fascial harvest: 8cm transverse incision 3cm above pubis, 6-8cm transverse incision made in fascia
      - ◆ underlying rectus separated from fascia, sling removed, attach to 0 Vicryl
      - ◆ sling width 1-1.5cm, taper ends: 6-8cm x 1.5cm
    - no data exist comparing absorbable vs. nonabsorbable suture
  - Develop retropubic tunnels
    - sweep rectus medially to identify triangular space lateral to muscle
    - transversalis fascia pierced w/ finger to enter retropubic space
    - may use Metz if scarred
  - Vaginal approach
    - weighted speculum placed, anterior vaginal wall 1/2 way from meatus and BN grasped w/ 2 Allis clamps
    - inject submucosal NS
    - inverted U incision, dissect vaginal mucosa from periurethral fascia
    - stay superficial to periurethral fascia
  - Sling placement and fixation
    - pass Stamey ligature carrier next to rectus, guided by finger in vaginal incision
    - unclamp Foley, look for hematuria
    - pull sling sutures through, so both ends of sling in retropubic space
    - sling sutured to periurethral fascia w/ 3-0 Vicryl
    - vaginal incision closed w/ running 3-0 chromic or Vicryl
  - Determination of sling tension
    - rectus closed w/ running 0 Vicryl
    - leave enough space for 2 fingers
    - urethral hypermobility, VLPP > 90: loose sling
    - ISD, VLPP < 90: tighter sling
    - severe ISD, VLPP < 60: compressive sling
      - ◆ can cross sutures in retropubic space prior to passing them through rectus fascia
- Post-op
  - vag pack: remove POD1
  - IV Toradol
  - Foley out POD1, unless bladder injury occurred (POD5-7 after cystogram)
  - teach CIC if needed
  - sex after 3-4 weeks

### What materials can be used for PVS?

- Autologous
  - rectus sheath
  - urethral wraps
    - rectus fascial free graft: like cuff of AUS
  - autologous fascia lata: skin incision b/w greater trochanter and lateral epicondyle of femur
    - smaller abdo incision, no chance of disease transmission, minimal cost
    - wider OR field, morbidity of thigh incision, pt repositioning after fascial harvest, increased risk of complications due to harvesting
  - vaginal wall slings
    - uses midline vaginal mucosa and underlying periurethral support structures to form sling
    - segment of vaginal mucosa overlying BN and urethra is isolated, retropubic space entered, and urethra and BN freed
    - suture through lateral edge of vaginal wall rectangle, transferred to SP incision over rectus
- Nonautologous
  - donor fascia lata
    - donors screened for: infection, ca, drug addiction, hepatitis, CVD, rabies, CJD, syphilis, HIV

## Chapter 32 Questions - PVS.doc

- graft acellular and sterile: solvent treatment, dehydration, irradiation, freeze-drying
- less complications as no need to harvest
- ?concerns re: quality of graft, potential for viral disease transmission
- human dermis, dura, pericardium: like fasciad
- Synthetics
  - monofilament polypropylene mesh (Marlex): no tension at BN to prevent erosions
  - monofilament polypropylene tape (TVT)
  - multifilamented polyester mesh (Mersilene): extremely high erosion rates
  - PTFE (Gore-Tex)
  - Silastic elastomer: high removal rates
  - collagen-injected woven polyester: high erosion rates

### What are the outcomes of pts w/ PVS?

- compared to baseline 15-30% prevalence rate for UI, w/ 10% "bothersome leakage"
  - very heterogeneous studies, lack of control groups, different definitions of cure
- Autologous rectus fascia slings: 90% continent at 4yrs, slightly higher w/ type II vs. type III SUI
  - Chaiken (1998): 23% persistent leakage, 3% de novo UI
- Autologous fascia lata slings: cure 70-90%
- Cadaveric fascia lata
  - Amundsen (2000): median F/U 20mo, 87% success, 1 retention, 15% de novo instability
  - allograft vs. autograft: similar cure rates of 71% vs. 77%
  - Radomski: 116 pts, only 3 pts w/ recurrent SUI at 1 yr, 59 pts after 2 yrs (only 5 pts have recurrent SUI)
    - no failures due to graft processing technique
- Vaginal wall slings: 97% cure rate at 1.5yrs
  - relies on ability of periurethral tissue to serve as the sling
- Combined autologous tissue sling procedures: 70-80% cured/satisfied
- Allogenic fascia lata slings: >90% cure rate
- Marlex slings: 77% cure rate at 5yrs, erosion rates not clear, new instability 5%
- TVT: excellent short term cure (3 yrs), no erosions yet
- Mersilene mesh slings: 95% cure at 2yrs
- Gore-Tex slings: cure 60% at 3yrs, 17% takedown due to retention
- Silicone: 71% cure rate, erosion rate 6%, 25% de novo instability

### What are the complications of PVS?

- see Chapter 31
  - osteitis pubis
  - erosion
  - retention
  - new onset instability
  - bleeding
  - infection
  - recurrent UI
  - fistulae

### What are the results from TVT?

- 80-90% cure rates
- less invasive
- TVT vs. Burch: no difference in continence, improved QOL w/ TVT
  - increased minor immediate complication rate
- 7 year results: 81% cured at 7yrs, 16% improved
- TVT vs. lap mesh: improved satisfaction w/ TVT
- TVT vs. SPARC: (Int Urogyn 2004): similar results, some poor voiding w/ TVT
  - no definite evidence that one is better than others

### What are the complications from TVT?

- bladder perf
- Fournier's

### What is the TOT?

- sling procedure through obturator foramen instead of retropubic space

**Chapter 32 Questions - PVS.doc**

- avoid vein, artery, nerve superolaterally
- not a loop: more laterally based
- shorter OR: 15min

**What are the results from TOT?**

- 85-90% cured at 12mo: similar to other vaginal tape procedures
- TOT vs. TVT: similar results, no vaginal erosion w/ either



### Chapter 33

## • Injection Therapy for Urinary Incontinence •

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#### How does injection therapy improve UI?

- improves ability of urethra to resist increases in Pabd w/o changing voiding pressure or Pdet
- restores mucosal coaptation and its "seal effect"

#### Where should the injectable be placed?

- bulking agents injected into urethral smooth muscle at the level of the **bladder outlet**
  - should be in lamina propria (Dmchowski)
  - intraurethral

#### What pts benefit most from injection therapy for UI?

- pts w/ SUI secondary to **ISD**, normal detrusor capacity and compliance, and **normal support**
  - pts that leak in supine position, bed wetting, leak w/ urgency
  - video UDS shows open BN at rest w/o detrusor contraction
- pts w/ combined ISD and hypermobility can be treated w/ injectables, but are better served w/ sling or AUS

#### What are the contraindications to injection therapy?

- active UTI
- untreated detrusor overactivity
- known hypersensitivity to injectable agent
  - hypermobility: not a contraindication, but are better served w/ PVS or AUS

#### How can one evaluate pts for injection therapy?

- Men
  - Hx: leakage w/ coughing, straining, exercise
  - UDS: r/o detrusor cause of UI
  - Cysto: r/o BN contracture
- Women
  - Px: Q-tip test to r/o hypermobility
  - stress test

#### What bulking agents are available for injection therapy?

- PTFE (Polytef, Urethrin)
  - due to **migration of PTFE particles and granuloma formation**, safety remains an issue
  - no reports of untoward sequelae in humans
  - no longer available
- Glutaraldehyde Cross-linked Bovine Collagen (GAX-Collagen)
  - bovine dermal collagen cross-linked w/ glutaraldehyde → resistance to collagenase digestion
  - no granuloma formation, no migration of particles
  - 95% Type I collagen, 1-5% Type III collagen
  - begins to degrade at 12mo, completely gone in 19mo
  - main problems are durability and antigenicity
- Durasphere
  - nonresorbable pyrolytic carbon-coated zirconium beads
  - larger (212-500um) than silicone or PTFE beads
  - encapsulate within tissue, retain bulk for >2yrs
  - no antigenicity
- Autologous injectables
  - blood, fat: no lasting quality → fat: 10-20% survives overall, 60% loss in 3 weeks
    - difficult to harvest, difficult to move (fragility of adipocytes)

### Chapter 33 Questions - Injections.doc

- requires very large needle for injection transurethraly
- cartilage
  - harvested from external pinna of ear
  - good responses:
- Silicone polymers: not going to be available
  - Macropastique/Bioplastique: textured polydimethylsiloxane macroparticles in povidone hydrogel
    - reasonable cure and improve rates, difficult to inject
  - disseminate throughout lung, kidney, brain in animal models

#### Describe the technique of injection therapy for UI.

- injections through cystoscope (transurethraly, men or women) or periurethraly (women only) w/ spinal needle
  - periurethraly: decreases bleeding complications, longer learning curve
- implant placed within wall of urethra
- local anaesthesia
- dermal skin test: for reaction w/ GAX-collagen
- Males
  - semilithotomy position, intraurethral lidocaine jelly, +/- perineal prostatic block
  - post-RP urethra usually scarred: several needle positions needed to deposit sufficient material
  - **needle must be proximal to external sphincter → injection into sphincter causes spasm and failure**
  - 4 quadrants, leave needle in for 30 sec to prevent extrusion
  - SP antegrade approach: via SP cystotomy dilated to 16F → can inject into supple, less scarred urethra
- Females
  - lithotomy position, jelly, infiltrate periurethral tissues w/ 2-4cc of 1% lidocaine
  - material **injected at BN and proximal urethra**
  - 0, 12, or 30-degree lens used
  - transurethral: needle advanced at 4 o'clock position, inject slowly, repeat at 8 o'clock
  - periurethral: needle within lamina propria, advances w/ minimal resistance
  - mucosal blebs meet at midline
- Postop
  - periop antibiotics
  - CIC w/ 10-14F catheter if retention, SP if long-term

#### What are the results after injection therapy for UI?

- no long-term follow-up available
  - PTFE: 70-95%
  - GAX-collagen: 65-95% (may be closer to 60%, rather than 95% - Dmochowski)
  - fat: 70-90%
  - silicone microspheres: 70-82%
- Males
  - after TURP: improvement or dryness in 88%
  - after RP: improvement or dryness in 67% (PTFE), 50-70% (GAX-collagen) at 1-2yrs
    - **poor results in post-RP men w/ UI**
- Females
  - PTFE: good short term results, some late local side effects (granuloma, urethral fibrosis) in 15%
  - fat: not reliable
  - silicone polymers: 82% cure in short term, 70% at 14mo
  - Durasphere: similar to GAX-collagen
  - GAX-collagen: 80% dry / significantly improved, 77% remain dry w/o need for 2<sup>nd</sup> injection
    - single injection of collagen vs. sling in Type II SUI (genuine SUI): cure 25% vs. 81%
    - 2-3 injections usually needed to achieve continence
    - efficacy in hypermobility comparable to women w/ classic ISD
- Paeds
  - myelodysplasia/sacral agenesis: 50% dry (2/4)
  - ISD from previous surgery: 86% cure
  - benefit kids w/ large bladder capacity and moderate ISD

#### What are the disadvantages to the use of injectables?

- inability to determine quantity of injectable needed
- safety of nonautologous products: migration, foreign-body reaction, immunologic effects

## Chapter 33 Questions - Injections.doc

### What are the complications of injection therapy for UI?

- Voiding dysfunction
  - retention
    - PTFE: 20%
    - GAX-collagen: 15%
  - new onset irritative voiding sx: 20% initially, resolve in few days
- Infection
  - UTI: 2%
  - balanitis
  - urethritis
  - epididymitis
  - abscess
- Fistula
- Trauma
  - hematuria
  - injection site injury
    - perforation and extravasation
- BOO
- pain at injection site
- spasm
- fat embolus: 1 death after fat injection
- migration

### What histologic reaction is seen after PTFE injection?

- histiocytic acute reaction, giant cell response, ingrowth of fibroblasts
- foreign body giant cell and granuloma formation

### What is the concern regarding migration of particles after injection?

- PTFE
  - particles in lymphatics and blood vessels, LN, lungs, brain, kidneys, spleen at 1 yr in animal models
  - mild allergic response seen
  - PTFE granuloma in lung in 2 pts
  - **no carcinogenic potential**

### What future injectables are being investigated for UI?

- Hylagel, Deflux: cross-linked HA
  - significant improvement vs. collagen: QOL, pad weights
- HA and dextranomer microspheres
- Uryx: injectable solution of ethylene vinyl alcohol copolymer dissolved in DMSO
  - DMSO diffuses and polymer precipitates
  - mid urethra to BN
  - slower injection vs. collagen
- Bioglass: biologically inert mix of Ca oxide, Ca silicone, and Na oxide
- Ca hydroxyapatite: as in bone and teeth (basically is sand)
  - interdigitates in soft tissue, no encapsulation
  - significant improvement in grade, pad weight reduction
- Urologen: suspension of collagen from skin banks
- Reprogenesis: chondrocytes harvested from ear, in alginate polymer
- implantable microballoons (Urovive)
  - sit next to BN and occlude urethra: external compression
- donor human collagen (non-self)
  - significant volume loss, not as good as bovine collagen
- dermis: inject as solid tissue

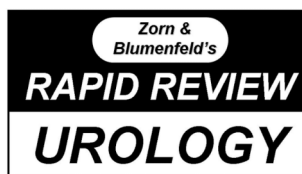
### What are the ideal characteristics for bulking agents?

- minimal fibrosis
- minimal extra-capsular inflammation
- minimal migration
- uniformity in size
- absolute minimum 110 microns



**Chapter 33 Questions - Injections.doc**

- should adhere to tissues
- appropriate carrier agent



## **Chapter 34**

### **• Implantation of the Artificial Urinary Sphincter •**

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#### **What are the indications for the AUS?**

- UI after RP
  - **need minimum 6mo b/w RP and placement of AUS**
- UI after pelvic #, urethral reconstruction, SCI
  - must have normal bladder compliance and contractility
- neurogenic bladder w/ sphincteric dysfunction
- congenital disorders
  - MMC
  - sacral agenesis
  - extrophy/epispadias
- females w/ neurogenic dysfunction whose condition responds poorly to conventional surgery
  - failed sling

#### **What is the site of AUS placement?**

- females: BN is only site for cuff placement
- male: bulbous urethra or BN
- kids: BN is only site for cuff placement
- intestinal segments: BN

#### **What are the contraindications for AUS?**

- Hostile LUT: any condition which would lead to high pressure storage and upper tract deterioration if outlet resistance ↑
  - Bladder
    - poor bladder compliance
    - low-volume detrusor hyperreflexia
    - DSD
    - bladder diverticulum
  - Outlet
    - unstable urethral/BN stricture
- Conditions requiring frequent instrumentation: increased risk for cuff erosion
  - recurrent bladder tumor
  - active stone disease
- Active infection: UTI, perineum, genital
- unwilling/unable to perform CIC
- young: age <6 boys of <9 girls; OK to perform at the same time as augment
- lack of manual dexterity/intelligence to work cuff

#### **How are pts evaluated prior to AUS insertion?**

- UDS + video
  - correct VUR if > Grade 2
- cystoscopy
  - r/o foreign body, false passage, strictures, diverticulae, contracture
  - wait 3 mo after TUIBN
- upper tract studies: usually IVP to r/o anatomic abnormalities

#### **Describe the technique of AUS insertion.**

- Pre-op
  - sterile urine C&S
  - antiseptic shower and limited bowel prep
  - consent
    - general points of consent

## Chapter 34 Questions - AUS.doc

- ± need for CIC
- reoperation/revision – 10%: mechanical repairs/adjustments or for complications
- ± need for removal w/ infx – 1-3%
- ± need for C-section (pregnancy OK, though); must be deactivated last trimester
- must take antibx before dental or surgical procedure
- long-term: must be motivated and reliable
- pre-op antibiotics
- skin scrub for 10min
- antibiotic irrigating solution
- Procedure
  - Male
    - midline perineal incision
    - identify bulbocavernosus muscle, dissect away from corpora cavernosum
      - ◆ do not injure urethra where it is attached to septum of corporal bodies at 12 o'clock
    - subcutaneous tunnel made to lower abdomen for reservoir
    - small transverse incision over lower rectus where pump to be placed
    - balloon reservoir placed in small pocket in prevesical space: 60-70cm H<sub>2</sub>O pressure reservoir
    - sphincter pump placed in dependent scrotum in dartos pouch
    - 8-14cm cuff usually in adult male
    - device tested 2-3X, deactivated for 6-8 weeks
    - incision closed in layers w/ absorbable sutures
  - Female
    - retropubic or transvaginal dissection
    - test bladder for tears w/ methylene blue
    - measure cuff: usually 6-8cm
  - Paeds: min age: 6 for boys, 8-9 for girls

### How does one deal w/ rectal/bladder injury during AUS placement?

- rectal injury: must abandon procedure
- bladder injury: repair in 2 layers if well-vascularized

### How does pregnancy affect AUS insertion?

- females of childbearing age: AUS not contraindicated
- elective C-section may be indicated to minimize risk of sphincter damage
- sphincter must be deactivated in 3<sup>rd</sup> trimester to reduce risk of erosion

### What are the complications of AUS insertion?

- Intra-op: anaesthetic related, medical, organ injury
- Immediate
  - post-op hematoma: may require drainage if large
  - retention: ensure cuff is fully deflated
  - post-op edema
  - early infection: usually *Staph epidermidis* and *Staph aureus*
- Late
  - proximal obstruction from stricture or BN contracture
    - must fully deactivate sphincter prior to treatment
    - if SP needed, place under fluoro guidance
  - infection
    - overall infection rate 1-3%
    - usually due to contamination at time of implantation
    - late infection: usually due to Gm- organisms
  - cuff erosion
    - usually 3-4mo after implant
    - presents w/ pain and swelling, UI, bloody discharge
    - must remove
    - higher incidence in pts w/ rads or neurogenic bladder
  - tissue atrophy
    - significant cause of UI
    - tx: reduce size of cuff, place more proximally, or place tandem cuffs
  - recurrent UI

### **Chapter 34 Questions - AUS.doc**

- must r/o VVF
- mechanical failures
  - leakage
    - ◆ lower cuff, then tubing, then reservoir
    - ◆ pump is least likely source of leakage
- erosion and infection occur more in kids

#### **What is the presentation and management of AUS infection?**

- pain, usually in scrotum near pump
- usually requires explant of entire mechanism
- can reimplant 3-6mo later

#### **What is the cause of cuff erosion?**

- unrecognized iatrogenic urethral injury
- infection
- tissue atrophy and mechanical failure

#### **What are the results from AUS insertion?**

- reoperative rate 12% in newer models





## Chapter 35

### • Surgery for VVF, Urethrovaginal Fistula, and Urethral Diverticulum •

#### What is the etiology for VVF?

- Congenital
  - extremely rare (Everett Urol 1957, Rousseau BJU 1996)
  - most occur at 8 wks and result from fusion anomaly of the distal portion of the Mullerian duct w/ UGS
  - commonly associated w/ other GU abnormalities
- Acquired
  - Iatrogenic
    - Surgical
      - ◆ gyne/pelvic surgery
        - ◆ TAH: **75% of all VVF in 1<sup>st</sup> world nations**, 1% in 3<sup>rd</sup> world
        - ◆ inadvertent suture incorporation of vaginal tissue from cuff closure into bladder wall
      - ◆ GI surgery: LAR, diverticular disease
    - Radiation
  - Non-iatrogenic
    - Birth trauma
      - ◆ most common cause in developing countries
      - ◆ due to tissue necrosis of bladder base from **prolonged labour**
    - Malignancy
    - Infectious disease
      - ◆ bilharziasis, TB
    - Foreign body: pessaries, diaphragm, IUD, catheter, stones
    - IBD, diverticulitis
    - autoimmune disease: Behçet's disease → vasculitis-related bladder wall necrosis

#### What RF increase risk of fistula formation after TAH?

| General              | Specific   |
|----------------------|--|
| 1. prior radiation   | 1. prior uterine/bladder surgery (incl. C-section) |
| 2. infection/PID/UTI | 2. intrinsic uterine disease: endometriosis        |
| 3. ischemia          | 3. prior cervical colonization (→ scarring)        |
| 4. atherosclerosis   | 4. use of pessary                                  |
| 5. DM                | 5. neurogenic bladder                              |
| 6. hypoestrogenism   | 6. voiding dysfunction                             |
| 7. hx steroid use    |  |

#### What are the clinical features of VVF?

- continuous urinary drainage from vagina after gyne or other pelvic OR
  - usually occurs 1-3 weeks after OR, longer delay if after rads
- ileus
- excessive pain
- hematuria

#### What are the causes of clear vaginal discharge after TAH?

- fistula: 0.1%-0.2% after TAH
  - urethrovaginal fistula
  - ureterovaginal fistula
  - vesicovaginal fistula
  - fistula b/w uterus and GU tract
- lymphatic leak
- peritoneal fluid leak
- fallopian tube fluid discharge
- urinary loss from bladder dysfunction

## Chapter 35 Questions - VVF, diverticula.doc

- detrusor instability or poor compliance
- ectopic ureteral drainage
- spontaneous vaginal secretions
- pus: vaginal infection
- pelvic tumour
- bladder stone (Deane, 2004)

### How does one evaluate the pt w/ suspected VVF?

- Px
  - Pelvic exam: vaginal capacity, mucosal integrity, induration, fibrosis
  - pooling of urine in vaginal fornices posteriorly
- Bloodwork
- Fluid for creatinine
- Pyridium test
  - intravaginal tampon after PO Pyridium + intravesical methylene blue
  - ureterovaginal fistula → orange tampon
  - VVF → blue tampon
- Cysto: **crucial!**
  - size and location of the fistula
  - assess bladder mucosa for edema
  - proximity to ureteral orifices
  - trace fistula w/ 5F ureteral catheter
  - biopsy of fistulous tract to r/o malignancy: either vaginal or cystoscopic approach
- Imaging: if fistula not visualized vs. perform in all cases
  - VCUG
  - IVP: assess upper tract for hydro or duplication, r/o ureteral involvement/obstruction
  - retrograde pyelogram, vaginography
- UDS: video UDS may show location
  - SUI (47%), detrusor instability (44%), and poor compliance (17%) may be seen (Hilton 1998)

### Where is the most common location for fistulous tract after TAH?

- at vaginal cuff

### What are the treatment options for VVF?

- Conservative management: may be tried regardless of timing
  - observation
  - antibiotics
  - catheter drainage
    - reasonable to try in all pts unless already tried → rarely successful
    - less likely to work in mature fistulae (>6 weeks old)
  - catheter drainage + electrofulguration of fistulous tract: don't use in large fistulous tracts
    - silver nitrate
  - physically abrading tract
  - suture closure of fistula via cystoscopy
  - adjuncts
    - anticholinergics
    - estrogen replacement
    - hyperbaric oxygen
- Surgical therapy
  - **fistulae identified within 48 postop can be operated on**
  - Formal repair: start all w/ cystoscopy
    - +/- tissue interposition: Martius flap, gracilis, gluteal, peritoneal, omentum
    - Preop considerations
      - ◆ timing of repair
      - ◆ abdominal vs. vaginal approach
      - ◆ excision vs. no excision of fistula tract
      - ◆ use of grafts or flaps for interposition
      - ◆ sexual function
      - ◆ presence or absence of SUI
      - ◆ postoperative drainage

## Chapter 35 Questions - VVF, diverticula.doc

- ◆ presence of radiated tissue
- ◆ need for concomitant procedures (augmentation cystoplasty, etc.)
- ◆ antibiotics, vaginal douche w/ antiseptic
- ◆ estrogen replacement if poor quality vaginal tissue
- Vaginal approach
  - ◆ anterior vaginal wall mucosal flap
    - ◆ interposition tissue from labia, peritoneum, or vaginal advancement flaps
  - ◆ weighted speculum + Foley placed
  - ◆ U or J shaped vaginal incision
  - ◆ fistula tract circumscribed, not widely excised → may create large defect
  - ◆ complete mobilization of vaginal wall away from edges of fistulous tract
  - ◆ tract closed w/ 2-0 or 3-0 Vicryl, 2<sup>nd</sup> closure layer in opposite direction, 3<sup>rd</sup> layer w/ vaginal wall
  - ◆ vag pack, SP, Foley
- Abdominal approach
  - ◆ midline or Pfannenstiel, bisect bladder to level of fistula: either intra- or extraperitoneal
  - ◆ mobilize bladder and vagina, and separate from each other
  - ◆ complete excision of fistulous tract
  - ◆ bseparate closure of vagina and bladder w/ Vicryl
  - ◆ omentum interposition graft
- Combined approach
- Colpocleisis: partial (Latzko) vs. complete
- Urinary diversion
- Post-op
  - SP + urethral Foley x 2-6 weeks
  - VCUG to confirm closure
  - anticholinergics until 2d prior to VCUG
  - estrogens to promote healing
  - avoid vaginal manipulation for 2/12

### What are the contraindications to electrofulguration of fistulous tracts as conservative management?

- large fistulae
- inflammatory, immature, or malignant fistulae

### What factors affect success of fistula repair?

- duration of fistula communication
- # of repairs
  - 1<sup>st</sup> repair most likely to succeed → 90% success rate (67-100%)
- etiology of tract: malignancy, rads
- presence of necrotic tissues
- surgical technique
- experience of surgeon

### What are the principles of VVF repair?

- watertight suture lines
- adequate exposure of tract
- well-vascularized tissue
- multiple layer closure
- adequate drainage of bladder: Foley + SPC x 2-3 weeks
- avoid cautery
- tension free
- nonoverlapping suture lines
- no infection
- interpositional tissue if repair tenuous
- **waiting period of 3-6mo: controversial → now individualized**
  - **fistulae identified within 48 postop can be operated on**
  - absolutely indicated in obstetric or radiation-related (complicated) fistulae
  - obstetric injury: 3-6/12
  - radiation-related: 1 yr (Wein Surg Gynecol Obstet 1980)

### What are the advantages and disadvantages of each surgical approach to VVF repair?



## Chapter 35 Questions - VVF, diverticula.doc

- vaginal surgery
  - difficult in pts w/ significant fibrosis, pelvic immobility, or large tracts near ureters
  - applicable to the vast majority of VVF
  - must have experience w/ vaginal surgery
  - less morbidity: quicker recover, less pain, avoid laparotomy and cystotomy
  - quicker: shorter operative time
  - avoidance of reentering operative field
  - versatile: multi-layer closure w/ interposition possible
  - concomitant transvaginal repair of incontinence possible
  - no compromise if subsequent abdominal attempt at repair required
  - consider even in complicated fistulae (radiation-induced or previously failed)
  - may be more difficult if visualization is impaired (stenotic vagina, no prior vaginal deliveries)
- abdominal approach: longer recovery, more morbidity
  - can be used for all bladder fistulas, except those extending into the urethra
  - Indications
    - pts requiring bladder augment or ureteral implantation
    - poorly visualized tract
    - narrow/immobile vagina, inadequate vaginal access
    - fistula near ureters
    - pt not able to undergo lithotomy
    - limited/no experience w/ transvaginal repair
    - intra-abdominal pathology requires simultaneous OR (post-radiation cystitis req. augment, bowel obstruction, enteric fistula)
    - giant or complicated (multiple,  $\geq 2$  organs involved)
    - prior unsuccessful repairs
    - difficult access: narrow vagina, anatomy difficult, poor access to high retracted fistula
      - ◆ may perform Schuchardt vaginal relaxing incision
    - versatility of intraperitoneal route
  - always better to move the ureter w/ reimplant rather than compromise the fistula repair

### What is a Martius flap?

- uses fibrofatty tissue of labia majora
- mobilized on pudendal or epigastric based pedicle
- graft tunnelled under vaginal wall to vaginal incision, sutured over repair w/ absorbable sutures
- small Penrose placed

### What is the Latzko method of proximal vaginal fistula repair?

- for pts that are poor operative candidates
- excise vaginal epithelium around fistula, + colpocleisis
- obliterates upper vagina
- do not excise fistulous tract

### What is the definition of a complicated VVF?

- fistula  $> 3$ cm in diameter
- recurrent fistula
- prior rads
- fistula associated w/ malignancy
- compromised area due to poor healing or host characteristics
- fistula at trigone, BN, urethra

### How does one manage the complicated VVF?

- interpositional tissues: labial flap, AP bladder flaps, myocutaneous flaps (rectus, sartorius, gluteus, gracilis)
- previous rads: biopsy to r/o malignancy

### What are the complications of VVF repair?

| Intraoperative   | Post-operative  |
|--|---|
| <ul style="list-style-type: none"><li>• bleeding</li><li>• ureteral injury</li><li>• adjacent organ injury<ul style="list-style-type: none"><li>→ ureter</li></ul></li></ul> | <b>Early</b> <ul style="list-style-type: none"><li>• vaginal infx</li><li>• bladder spasms (anticholinergics)</li><li>• bleeding (vag pack, bed rest)</li></ul> |

## Chapter 35 Questions - VVF, diverticula.doc

### Delayed

- vaginal shortening and stenosis
  - ureteral injury + ureteral obstruction
  - leak/recurrence of fistula
  - dyspareunia from cicatricial vaginal stenosis
  - treat w/ relaxing interpositional vaginal grafts
- 

### How does one harvest a gracilis flap?

- skin incision over medial aspect of leg
  - from medial condyle of femur to inferior pubis
- distal insertion transected
- muscle dissected proximally, avoiding neurovascular pedicle injury
- place in tunnel from thigh to vaginal wall
- ion
- vaginal stenosis

### What are the causes of urethrovaginal fistulae?

- see above
  - usually prior gyne surgery
  - prolonged catheter drainage
  - birth trauma

### What is the major difference b/w repair of VVF vs. urethrovaginal fistula?

- urethrovaginal fistula not excised → circumscribed and oversewn (like urethrocuteaneous fistulae)
  - excision of tract will increase the defect and make the closure more difficult

### What is involved in the evaluation of pts w/ urethrovaginal fistulae?

- as above
- Px: extent of urethral loss, pelvic organ prolapse, atrophic vaginitis, objective SUI
- Urethroscopy: exclude involvement of bladder or trigone
- Imaging
  - VCUG
  - US abdomen

### Describe the management of urethrovaginal fistulae.

- small/intermediate fistulae: tension-free layered closure
- distal fistulae
  - small: extended meatotomy or primary closure
  - large (>1cm): paravaginal flap/interpositional graft +/- sling
- proximal urethra/BN
  - small: paravaginal flap/interpositional graft +/- sling
  - large (>1cm): BN reconstruction +/- paravaginal flaps/interpositional graft +/- sling
    - BN closure and diversion if ++ tissue loss and no reasonable periurethral tissues for reconstruction
    - usually require sling → **do not do mesh sling: fascial slings only**

### Describe the operative technique for repair of urethrovaginal fistula.

- Procedure
  - lithotomy, Foley, SP
  - anterior vaginal wall flap raised w/ inverted U incision
  - dissect to level of BN
  - dissect laterally if needed to enter retropubic space for sling
  - fistula tract circumscribed, but not excised, margins opposed w/ 3-0 or 4-0 locking running absorbable
  - remove redundant vaginal epithelium
  - 2<sup>nd</sup> layer w/ overlying periurethral fascia
  - interpositional tissues if closure lines or vaginal tissues in question
- Post-op
  - antibiotics and anticholinergics
  - catheter x 10d
  - VCUG
  - do not attempt to recatheterize

## Chapter 35 Questions - VVF, diverticula.doc

### What options are available for urethral reconstruction w/ fistula?

- abdominal approach
  - posterior bladder flaps
  - anterior bladder flap
  - omentum to reinforce
- vaginal approach +/- Martius labial interposition
  - paravaginal flaps
  - meatal based vaginal flap
  - vaginal advancement flaps
- combined abdominovaginal approach
  - anterior bladder tube neourethra
  - rectus abdominis flaps
    - recommended as salvage after failed Martius flap
  - perineal-based flap
- BN closure w/ diversion

### Describe the operative technique for vaginal flap urethral reconstruction.

- Paravaginal flaps
  - lithotomy, 20F SP, 14F Foley
  - inverted vaginal U incision w/ apex just proximal to meatus
  - neourethra created w/ 2 parallel incisions on either side of urethral meatus
  - flaps mobilized laterally and tubularized around 14F catheter w/ locking 4-0 absorbable suture
  - reinforce suture lines w/ labial flap
  - close vaginal labial tissues
  - sling (if needed) placed w/o tension
  - vag pack, leave SP and Foley

### What is meant by the "giant fistula?"

- extensive lesion >5cm in diameter
- standard repair as previous, use augment if significant loss of bladder capacity

### What are the complications of urethrovaginal fistula repair?

- inability to void
  - leave SP, drain intermittently → avoid urethral catheterization for 8-12 weeks
- incontinence
  - bladder instability vs. ISD vs. fistula recurrence

### What is the incidence of urethral diverticulum?

- 1-5% in general pplx
- 1.4% in women w/ genuine SUI
- seen in 3<sup>rd</sup>-6<sup>th</sup> decade of life

### What is the etiology of urethral diverticulum?

- congenital: most rare
  - Gartner's duct remnants
  - dilated periurethral cysts
  - associated w/ blind-ending ureters
  - aborted urethral duplication
  - faulty union of primordial urogenital sinus folds
  - Mullerian cell rests
- acquired
  - urethral trauma
    - childbirth
    - instrumentation or dilation
  - recurrent infection: obstruction followed by dilation and rupture of urethral glands into lumen
    - most common organisms: *E. coli*, *Chlamydia*, *N. gonococcus*

### What findings are often associated w/ urethral diverticula?

- malignancy

### Chapter 35 Questions - VVF, diverticula.doc

- most common type is **adenocarcinoma**, then TCC: SCC rare
- tx: wide local excision w/ radiation therapy
- outlet obstruction
  - stricture?
- stones: in 1-10% of pts, usually struvite
- infections
  - 1/3 pts w/ urethral diverticula have recurrent UTI
- UI: seen frequently
  - due to genuine SUI or paradoxical incontinence (UI due to intermittent drainage of diverticulum)

### What is the presentation of urethral diverticula?

- Hx
  - **3 D's**
    - **dysuria**
    - **dribbling (PVD): in 25%**
    - **dyspareunia**
  - asymptomatic
  - LUTS
  - UTI: in 50%
  - hematuria
  - swelling
  - anterior vaginal wall pain
- Px
  - 63% of cases will be diagnosed by P/E
  - anterior vaginal wall mass
    - compression causes discharge of purulence/blood from urethra

### What is the DDx of anterior vaginal wall mass?

- ureterocele
- Gartner's duct cyst
- Mullerian remnant cyst
- vaginal wall inclusion cyst
- urethral/vaginal ca
- Skene's gland cyst

### How can one classify urethral diverticulae?

- Leach L/S/C3 system
  - Location
  - Size
  - Configuration, Communication, Continence
- Diverticula vs. Pseudodiverticula
  - pseudo: more commonly associated w/ prior urethral surgery and UI → need sling

### How can one evaluate pts w/ urethral diverticula?

- Hx/Px
- Cysto
  - simultaneous vaginal exam to compress anterior vaginal wall to extrude diverticular contents
  - diagnostic in 95%
- Imaging
  - VCUG
  - transvaginal US: more sensitive than VCUG
  - MRI
    - extremely sensitive: ?gold standard
  - retrograde +ve pressure urethrography: diagnostic in 90%
    - difficult to learn, painful
  - upper tract imaging: if concern of ectopic ureterocele
- UDS
  - in pts w/ symptomatic UI or PVD

### What techniques are available for surgical treatment of urethral diverticulum?

### Chapter 35 Questions - VVF, diverticula.doc

- endoscopic
  - incise urethral floor w/ cold-knife
    - use only for distal diverticula → proximal lesions may cause UI from smooth muscle injury
- Spence procedure: distal urethral marsupialization → essentially a meatotomy
  - may cause septum that causes dyspareunia
- transvaginal excision

#### What ways can one identify diverticulum location for noninflamed decompressed diverticula?

- pack w/ gauze
- pass Foley into ostium
- inject w/ fibrin clot mix or cellulose
- place Fogarty embolectomy catheter

#### Describe the technique of transvaginal urethral diverticulum repair.

- Procedure
  - Foley, SP
  - anterior vaginal U shaped incision
  - lateral dissection to endopelvic fascia if need sling
    - no increased risk of infection
  - flap mobilized to BN
    - periurethral fascia and tic remain undissected until complete vaginal wall mobilization completed
  - proximal and distal periurethral fascial flaps developed
  - dissect circumferentially down to level of diverticular communication w/ urethra
  - urethral communication opened and tic removed at ostium
    - w/ large tics, may undermine trigone
    - may leave proximal tic if complete urethral communication w/ tic removed
  - vertical urethral mucosal locking closure w/ 4-0 synthetic absorbable suture
  - close periurethral fascia in 2<sup>nd</sup> layer 2/ transverse 3-0
    - fat-pad interposition graft if 2<sup>nd</sup> layer poor
  - vaginal wall closed w/ running 2-0 absorbable
  - vag pack
- Post-op
  - IV antibiotics for 24h, PO until Foley out, O&B suppositories
  - vag pack out POD1
  - VCUG POD14

#### What are the complications of urethral diverticulum repair?

- Intra-op
  - bleeding
  - inability to find diverticulum
- Post-op
  - infection
    - recurrent UTI (10-30%)
  - recurrent diverticulum (0-20%)
  - fistula (5%)
  - SUI (2-15%)
  - urethral stricture (2%)
  - urethral stenosis from overresection of tic
  - persistent pain/dyspareunia



## **Chapter 36**

### **• Geriatric Incontinence and Voiding Dysfunction •**

---

#### **What is the incidence of UI in the elderly?**

- 15-30% elderly at home
- 33% elderly in acute care settings
- 50% in nursing homes

#### **What are the complications of UI in the elderly?**

- perineal rashes
- pressure ulcers
- UTI
- urosepsis
- falls and fractures
- depression/embarrassment

#### **How does the lower urinary tract change w/ age?**

- bladder contractility, capacity, and ability to postpone voiding decline in M and F
- urethral length and MUCP decline in F
- prostate enlarges in M
- prevalence of involuntary contractions increases
- PVR increases
- fluid excretion occurs mostly at night

#### **What are the causes of transient incontinence in the elderly?**

- **Mnemonic - DIAPPERS**
  - Delirium/Confusion
  - Infection
    - if ++ dysuria/urge, pt not able to reach toilet before voiding
  - Atrophic vaginitis (urethritis)
    - mucosal atrophy, friability, erosions, hemorrhages
    - mimics UTI
    - tx: low dose estrogen PO or PV 0.3-0.6g OD
      - ◆ decreases dyspareunia and UTI recurrence
      - ◆ contraindicated in women w/ hx of breast ca
  - Pharmaceuticals
  - Psychologic disorder (esp. depression)
  - Excess urine output
    - due to excess fluid intake, diuretics, metabolic abnormalities (hyperglycemia), fluid overload (CHF)
  - Restricted mobility
    - arthritis, hip deformity, deconditioning, postural hypotension, claudication, spinal stenosis, CHF, poor eyesight, fear of falling, drug-induced disequilibrium, confusion
  - Stool impaction

#### **What medications commonly affect continence in the elderly?**

- Sedatives/hypnotics
  - cause sedation, delirium, immobility
- Alcohol
  - polyuria, frequency, urge, sedation, delirium, immobility
- Anticholinergics
  - retention and overflow, detrusor instability from chronic retention, dry mouth and increased fluid intake
- Antipsychotics
  - anticholinergic, sedation, rigidity, immobility
- Antidepressants

## Chapter 36 Questions - Geriatric UI.doc

- anticholinergic, sedation
- Anti-parkinsonians
  - anticholinergic, sedation
- Narcotics
  - retention, constipation, sedation, delirium
- $\alpha$ -blockers
  - SUI in women
- $\alpha$ -agonists
  - retention in men
- CCB
  - retention, nocturnal diuresis from retention
- Diuretics
  - polyuria, freq, urge
- ACEi
  - drug-induced cough leads to SUI
- Vincristine
  - retention

### What are the causes of non-transient (established) incontinence in the elderly?

- detrusor overactivity
  - most common type of lower tract dysfunction in elderly
  - detrusor hyperreflexia (associated w/ CNS lesion) vs. detrusor instability (no CNS lesions)
- DHIC (detrusor hyperactivity w/ impaired contractility)
  - most common form of detrusor overactivity in elderly
  - coexistence of detrusor overactivity and weakness
  - often see retention, esp w/ anticholinergics
  - mimics all other causes of UI
  - may be associated w/ urge, freq, weak flow, increased PVR, trabeculation
- SUI
  - 2<sup>nd</sup> most common cause of UI in older women
  - ISD: from operative trauma or urethral atrophy
  - men: usually post-RP
- urethral instability
  - sphincter paradoxically relaxes in absence of contraction
- BOO
  - 2<sup>nd</sup> most common cause of UI in older men
  - rare in women: usually kinking w/ cystocele or post-sling
- detrusor underactivity
  - widespread degeneration of muscle cells and axons
- functional incontinence
  - UI unrelated to lower urinary tract
  - implies normal lower tract, w/ UI due to cognition and mobility
  - normal urinary tract is the exception in the elderly

### What changes exist at the cellular level in pts w/ detrusor overactivity?

- "complete dysjunction pattern"
  - widening of intercellular space
  - replacement of normal intermediate muscle cell junctions w/ novel "protrusion" junctions and "ultraclose abutments"
  - change in cell coupling from mechanical to electrical mechanism

### How does one investigate elderly pts w/ incontinence?

- Hx
  - transient causes: DIAPPERS
  - Meds
  - functional impairment
  - ADLs and IADLs
  - voiding pattern and type of UI
  - precipitancy = abrupt sensation that urination is imminent, whatever follows
  - LUTS

## Chapter 36 Questions - Geriatric UI.doc

- bother
- Voiding diary: 48-72h
- Px
  - neurourologic exam
  - atrophic vaginitis
  - peripheral edema
  - DRE: impaction, masses, reflexes, prostate
  - Qtip test
  - Bonney/Marshall test
- Labs
  - lytes, BUN, Cr, glucose, Ca
  - U/A, urine C&S, cytology
- UDS
  - stress test: one single cough or strain
    - SUI: immediate leakage, stops w/ abdominal relaxation
    - stress-induced detrusor overactivity: delayed leakage
  - PVR: measured within 5min of voiding
    - search for hydro if PVR > 200cc
  - uroflow

### What are the causes of nocturia?

- Volume related
  - age-related
  - excess intake/alcohol
  - diuretic, caffeine, theophylline
  - endocrine/metabolic
    - DM/DI
    - hypercalcemia
  - peripheral edema
    - CHF
    - low albumin states
    - PVD
    - meds: Li, NSAIDs, nifedipine
- Sleep related
  - insomnia
  - pain
  - dyspnea
  - depression
  - drugs
- Lower urinary tract related
  - small capacity bladder
  - detrusor hyperactivity
  - prostate related
  - overflow
  - decreased compliance
  - sensory urgency

### What is the treatment for UI in the elderly?

- Detrusor overactivity w/normal contractility
  - behavioural therapy: bladder retraining, prompted voiding
    - pressure stockings if CHF, change diuretic schedule
  - adjuncts: pads, special undies
  - condom catheters
  - medical tx: anticholinergics, smooth muscle relaxant, or CCB if needed and not contraindicated
    - try imipramine, avoid TCAs
    - avoid vasopressin: causes ARF, CHF, hyponatremia, fluid retention
  - induction of retention + CIC
    - can add CIC at bedtime
    - indwelling not helpful: spasms and bypassing
- DHIC



### Chapter 36 Questions - Geriatric UI.doc

- if emptying w/ straining, behavioural therapy as above
- if PVR > 150cc, augmented voiding techniques: Crede, Valsalva, double voiding → only after voiding begins
- can add medical therapy
- CIC
- SUI
  - behavioural therapy, weight loss, treat cough or atrophic vaginitis
  - Kegels
  - vaginal cones, biofeedback, electrical stimulation
  - imipramine or  $\alpha$ -agonists
  - surgery: sling, AUS, injection therapy
  - condom catheter or penile clamp in men
- BOO
  - behavioural therapy
  - bladder relaxants if coexistent detrusor overactivity and PVR small
  - $\alpha$ -blockers: can cause symptomatic hypotension
  - finasteride, antiandrogens, LHRH agonists
  - surgery: TURP, TUIP
- Underactive detrusor
  - decompress x weeks, then do voiding trial → reverse potential contributors (meds, constipation)
  - if PVR large (or in retention), try augmented voiding techniques (Crede, Valsalva, double voiding) or  $\alpha$ -blocker
  - if fails TOV, CIC or indwelling

### What are the complications from chronic indwelling catheters?

- UTI: pyelo, urosepsis
- bladder and urethral erosions
- bladder stones
- cancer

### What are the indications for catheterization in the elderly?

- acutely ill pt to monitor fluid balance
- nonhealing pressure ulcer
- decompression for pts in retention
- overflow UI refractory to other measures

### What steps are important prior to removing an indwelling Foley?

- decompress x 1-3 weeks
- correct reversible causes of retention: constipation, pain, anticholinergics,  $\alpha$ -agonists, CCB
- treat delirium, depression, atrophic vaginitis, UTI
- record urine output x 2d to establish normal u/o
- insert catheter only after pt voids to get PVR, or if pt cannot void
- measure PVR
  - if PVR > 400, reinsert Foley and evaluate
  - if PVR 100-400cc, watch for delayed retention

### What are the principles of indwelling Foley care?

- maintain sterile closed gravity system
  - empty q8h, rotate site of attachment q3d, don't routinely irrigate catheter, don't clamp/kink tubing, avoid frequent cleaning of urethral meatus
- if spasms, decrease balloon size or add bladder relaxant
- don't give antibiotics as prophylaxis
- no C&S surveillance needed
- if symptomatic UTI, change Foley before getting C&S → cultures through old cath will be colonizations
- if ++ encrustation, consider urine acidification or treatment for *Proteus*
- change cath q1-2mo, or less frequent if patent and pt complication-free



## Chapter 37

### • **Molecular Biology, Endocrinology, Physiology of Prostate and SVs** •

---

#### **What substances appear in the seminal plasma?**

- fructose
- citric acid
- spermine
- PGs
- proteins
- Zn
- enzymes: Ig, proteases, esterases, phosphatases

#### **What are the potential roles for seminal plasma?**

- provide buffer
- increase sperm motility and survival
- enhancing sperm transport
- extension of sperm viability and decrease environmental shock

#### **Describe the embryonic development of the prostate.**

- **Wolffian ducts develop into SVs**, epididymis, vas, ampulla, and ejac ducts
  - stimulated by fetal T, not DHT
  - completed by 13<sup>th</sup> week
- **prostate develops from urogenital sinus** in 3<sup>rd</sup> month
  - stimulated by DHT
- 5 epithelial buds form on posterior UGS on both sides of veru
  - invade mesenchyme to form the prostate
  - top pairs of buds form inner zone of prostate → mesodermal origin: gives rise to BPH and TZ
  - lower buds form outer zone of prostate → endodermal origin: gives rise to PZ and prostate ca
  - develop as concentric circles around urethra
- prostate forms acini and collecting ducts by arborization
- extensive squamous metaplasia appears that peaks at 36 weeks, then subsides
  - causes decrease in prostate size at 3 months
- DHT produced from T by epithelium and mesenchyme
  - epithelium makes more DHT → may diffuse to stroma
  - stromal cells have larger amounts of androgen R: ?exclusive to mesenchyme during development
    - DHT may be formed by epithelial cells and diffuses into stroma
- MIS expressed early in gonadal differentiation, and causes regression of Mullerian structures
  - required for virilization

#### **Describe the postnatal development of the prostate.**

- at birth, prostatic acini lined by squamous epithelium
  - postnatal development under control of residual maternal steroids
  - postnatal prostatic involution occurs over 1<sup>st</sup> 5 mo
- neonatal surge in T b/w 2-3 months
  - can reach adult serum T range
- neonatal and prepubertal steroids needed to set long-term growth regulation of the prostate

#### **What different cell types exist in the prostate?**

- epithelial cells → all rest on the BM, which surrounds the acini
  - secretory epithelial cells
    - columnar, abundant secretory granules and enzymes that **stain abundantly w/ PSA, PAP**, other enzymes
    - connected by CAMs w/ their base attached to a BM through integrin R, nucleus at base below Golgi
    - non-dividing

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- basal/stem cells (<10% of cells)
  - much smaller and fewer than epithelial cells, round, little cytoplasm and large nuclei
  - rich in keratins, devoid of secretory products → **stain for HMW cytokeratin** (34-β-E12)
    - ◆ acini of prostatic adenocarcinoma do not have basal cells and don't stain for HMW cytokeratin
  - sit on BM
  - may serve a proliferative role
- neuroendocrine cells (APUD cells – amine precursor uptake decarboxylase cells)
  - found in epithelium of acini and ducts of all parts of gland, and in urothelium of prostatic urethra
  - 3 types of neuroendocrine cells:
    - ◆ major type: contains serotonin and TSH, 2 minor types: contain calcitonin and somatostatin
  - involved in regulation of prostatic secretory activity: may be stimulated by cholinergic R
- other cell types suggested: immature nonsecretory glandular cell, nonsecreting predegenerative glandular cell, and degenerating glandular cell
- stroma cells
  - smooth muscle
    - clustered around acinar structure: involved in mechanical expression of ejaculate fluid
  - fibroblast
  - endothelial cells

### What are the components of the tissue matrices of the prostate?

- Extracellular
  - BM: type IV and V collagen mesh, laminin-rich, fibronectin
    - laminin: extracellular matrix protein, anchors epithelial cell to BM, **produced by epithelial cells** (not by fibroblasts)
      - ◆ binds integrin-type R
      - ◆ changes its isoform during neoplastic transformation
    - fibronectin: **secreted primarily by prostatic fibroblasts**, forms adhesive material
      - ◆ binds integrin-type R
  - connective tissue: type I and III fibrillar collagen, elastin
  - GAGs: dermatan (40-50%), heparin (20%), chondroitin (16%), HA (20%)
- Intracellular (cytomatrix)
  - network of microtubules (tubulins – 20nm), intermediate filaments (keratin, desmin, vimentin – 10nm), and microfilaments (actins – 6nm)
    - tubulin: anchors cellular structures, determines cellular shape
    - desmin: central component of all muscle cells
    - vimentin: found in all fibroblasts
  - terminates in center of cell by direct attachment to nuclear matrix
- Intracellular (nuclear matrix)
  - DNA tight-binding proteins, RNA, residual nuclear proteins

### Describe the endocrine control of prostatic growth.

- hypothalamus releases LHRH (or GnRH)
- LHRH causes pituitary to release LH → acts on Leydig cells in testes to stimulate steroid synthesis and T release
  - T is major serum androgen stimulating prostate growth
  - peripheral conversion of T by aromatization forms estrogens in male
- ACTH release by pituitary stimulates adrenal androgen androstenedione
  - minor role in regulating prostatic growth
- PRL release by pituitary lactotrophs
  - may enhance uptake of androgens into prostate, and to affect citric acid synthesis
- estrogens created by peripheral aromatization cause direct –ve feedback effect on LH production in pituitary
  - reduces T production in testis

### How are androgens produced in the testes?

- Leydig cells stimulated by LH to synthesize T from acetate and cholesterol
  - T concentration in gonadal vein is 75X serum levels
- average T concentration in adult male: 10-35 nmol/L
- 2% of total T free in plasma → available for uptake for metabolism to DHT

### What is the active form of androgen in the prostate?

- DHT → irreversibly formed by 5α-reductase: 2 isozymes in human
  - Type I: predominates in skin, liver, prostatic epithelium, and prostatic fibromuscular stroma

## Chapter 37 Questions - Prostate physiology.doc

- involved in hair formation
- Type II: in basal cells of epithelium and in stromal cells
- absent in secretory epithelial cells
- androgens stimulate expression of type II gene, but not type I
- DHT inactivated by being irreversibly hydroxylated to inactive triols

### How do adrenal androgens stimulate prostatic growth?

- hyperstimulation of adrenal cortex can cause overproduction of adrenal steroids → can stimulate prostatic growth
- adrenalectomy has little impact on prostatic size
- threshold level of DHT required for prostatic growth → castrate level is below this threshold
- DHEA and DHEAS: form < 1% of total T in plasma

### What is the origin of estrogen in the male?

- small amounts produced directly by testes
  - Sertoli cells produce small amount of estrogen w/ FSH stimulation
- 75-90% derived from peripheral conversion of androstenedione and T → estrone and estradiol via aromatization
- most of daily production involves adipose tissue

### How are androgens bound in the plasma?

- 98% reversibly bound to serum proteins
  - albumin: binds 40% of T
  - SHBG [TeBG, or SBG(steroid-binding globulin)]: binds 57% of T
  - CBG (corticosteroid-binding globulin, aka transcortin): binds <1% of T
  - PBG (progesterone-binding globulin)
  - AAG ( $\alpha_1$ -glycoprotein)
- < 2% is free or unbound

### What factors affect amount of steroid bound to proteins?

- affinity of steroid to bind
  - albumin: low affinity for T
  - SHBG: high affinity, low concentration
- capacity (amount of binding protein in plasma)
  - albumin: can bind large volumes of T due to high concentration

### How can plasma levels of SHBG be altered?

- T administration: decreases SHBG levels
- estrogens: stimulate SHBG levels, increasing T binding, lowering free T concentration, decreasing entrance into cells
  - increases ratio of free estradiol to free T

### What are the steps involved in T action at the cellular level?

- cellular uptake of T
- T conversion to DHT: irreversible
- DHT binding to androgen R in cytoplasm
  - subjected to a series of reversible reactions: forms  $3\alpha$ -diol (strong androgen) and  $3\beta$ -diol (weak androgen)
  - can be inactivated by irreversible hydroxylation to inactive triols
- activation of steroid R
- nuclear transportation of activated androgen R
- DHT receptor interacts w/ nuclear R
- stimulation of expression of tissue-specific genes

### What is the role of estrogen in prostate growth?

- estrogens increase androgen nuclear R in prostate cell
- stimulate stromal elements of prostate
- cause squamous cell metaplasia in prostate growth

### Where is the androgen R gene?

- long arm of X chromosome: Xq11-13

### What are the steps of activation of the androgen receptor?

- initial complex formation w/ chaperonins

### Chapter 37 Questions - Prostate physiology.doc

- after production of protein in ribosome, R forms complexes w/ chaparonins (8S complex)
- occurs before activation by ligand binding
- binding of ligand (T or DHT)
  - affinity for DHT much higher
- activation of the R w/ post-translational modification
  - androgen binds to steroid and dissociates from chaparonin complex
  - receptor phosphorylation occurs
- dimerization
- nuclear localization
  - androgen R transported to nucleus across nuclear pore complex involving 2 nuclear localization signals (NLS)
  - requires multiple steps: binding NLS to importins, docking to nuclear pore, translocation, GTP-mediated release
- binding of R to coactivator complexes → regulate gene expression
  - binding to antagonist (ex: flutamide): histone acetyltransferase activity inhibited, gene repressed
  - binding to agonist: histone acetylation and activation of gene expression
- AR-dependent chromatin remodeling
  - steroid receptor complex can only interact w/ genes in "open" regions
  - receptor SWI-SNF complex opens structure of chromatin to allow transcription

### What is the role of the nuclear matrix in androgen action?

- important role in DNA organization
  - DNA organized in unique 3D array in different cell types
  - determined by nuclear architecture and scaffolding of nuclear matrix
- matrix is target for androgen and estrogen R binding
  - 60% of all nuclear ARs associated w/ nuclear matrix
- role in DNA replication
  - contains fixed sites for DNA synthesis
  - associated w/ mRNA synthesis during transcription

### What are the different types of cellular adhesion molecules (CAMs)?

- integrins: link cell to BM and ECM components through heterodimer interactions
  - made of 2 covalently linked heterodimers:  $\alpha$  and  $\beta$  subunits
  - externally contact ECM R of fibronectin, fibrinogens, collagen, laminin, and GAGs in ECM
- cadherins: link cell to neighbouring cells, through homotypic polymers
  - 3 subtypes:
    - E-cadherins: bind prostate epithelial cells to each other
      - ◆ **reduced or absent in high-grade prostate cancer**
    - N-cadherins: found in neural tissues
    - P-cadherins: in placenta and epithelium
- selectins: link cell to carbohydrate moieties
  - primarily on vascular system
- Ig superfamily adhesion molecules

### What is the role of vitamin A and D in normal prostatic function?

- Vitamin A
  - can **protect** against development of prostate cancer
  - is a retinol: natural and synthetic analogues are called retinoids
  - inhibit growth of normal and cancerous prostate cells
- Vitamin D
  - is a steroid
  - stimulates levels of IGF binding protein in prostate cancer
  - induces columnar differentiation
  - enhances growth and differentiation of prostate

### What growth factors exist in the prostate?

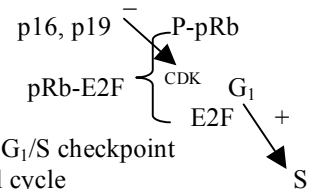
- fibroblast GF (FGF)
  - 9 polypeptides in FGF family: FGF2 important in prostate → mitogen for prostate stromal cells, weak for epithelial cells
- epidermal GF (EGF)
  - localized to secretory epithelium, receptors in basal neuroendocrine cells → androgen independent
  - does not play a functional role in androgen-stimulated growth of prostate cells
  - erb-B2/neu oncoprotein: closely related but not identical to EGF R

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- TGF- $\alpha$ 
  - stimulates growth of prostate ca in culture
- TGF- $\beta$ 
  - TGF- $\beta$ 2 increased in BPH, TGF- $\beta$ 1 is not
  - may function as braking system in normal prostate
  - TGF- $\beta$ 1 inhibits epithelial cell growth by blocking entrance into S phase
- bone morphogenic proteins
- IGF-I and -II (somatomedin)
  - PSA (protease) cleaves IGF-BP to release free form of IGF
  - prostate epithelial cells contain type II GF R, stromal cells synthesize and secrete IGF II
- PDGF
  - mitogenic effect on mesenchymal and CT cells
- endothelins
  - constrict blood vessels and increase BP
  - ED-1 is a prostate cancer mitogen

### What is the function of the retinoblastoma gene (Rb)?

- general controller of the cell cycle
  - when it is not phosphorylated, binds to nuclear matrix and inhibits cell proliferation by acting at G<sub>1</sub>/S checkpoint
  - when the Rb protein is phosphorylated, it releases the brake and allows cell to move through cell cycle
- pRb is normally complexed to E2F
  - phosphorylated by cyclin-dependent kinases, which drives transitions of the cell cycle
  - phosphorylated pRb dissociates from E2F, allowing uncomplexed E2F to induce transit from G<sub>1</sub> to S phase
- if p53 is induced at the G<sub>1</sub>/S checkpoint, p16 and p21 CDK inhibitors are induced, arresting cell division



### How does castration affect prostatic cell population?

- causes 90% loss in total # of prostatic epithelial cells
- slower and less complete reduction of 40% of prostatic stromal cells

### What glands form the bulk of the seminal plasma?

- Initial fraction
  - prostate: 0.5cc
  - Cowper's gland: 0.1cc
- Final fraction
  - SVs: 1.5-2cc
  - glands of Littre: 0.1cc

### What are the nonpeptide components of prostatic secretions?

- citric acid
  - formed in the prostate at 100X higher concentration than in other tissues
  - results from inability of prostate cell mitochondria to oxidize citrate
  - binds metal ions
- fructose
  - source of fructose in seminal plasma is SVs: other small amounts of free sugars (glucose, sorbitol, ribose)
    - pts w/ absence of SVs have no fructose
  - produced from glucose → sorbitol by aldose reduction, then ketone reduction → fructose
  - source of energy for sperm
- polyamines
  - spermine and spermidine → originate mostly from prostate
    - oxidized by diamine oxidase to form aldehyde compounds that are toxic: forms odor of semen
  - 1<sup>st</sup> and rate-limiting step in polyamine synthesis is ODC (ornithine decarboxylase)
  - inhibited by DFMO (difluoromethyl ornithine) → has been used for prevention of prostate cancer
- phosphorylcholine
  - substrate for PAP
  - rapid formation of free choline in 1<sup>st</sup> ejaculate
- PGs
  - primarily from SVs, not prostate as the name suggests
  - 15 types of PGs in prostate, divided into 4 groups: A, B, E, F
    - subdivided according to position and # of double bonds in the side chain (ex: PGE<sub>3</sub> → 3 double bonds)
  - wide variety of effects: erection, ejac, motility, affect cervical mucus

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- cholesterol and lipids
  - stabilize sperm against temp and environmental shock
- Zn
  - levels increased or stable in BPH, decreased levels in prostate ca
  - may have role in antibacterial factor

### What protein in the seminal fluid causes seminal coagulation?

- semenogelin: predominant SV-secreted protein

### What are the secretory proteins of the prostate?

- PSA
  - serine protease, found almost exclusively in epithelial cells of prostate
  - member of human kallikrein gene family:
    - hKLK1
    - hKLK2: prostate-specific serine protease closely related to PSA
      - ◆ hK2 cleaves pro-PSA to generate active PSA
    - kKLK3 = PSA
    - kKLK-L1
  - PSA complexed to ACT in serum, as well as MG
- PSMA (prostate-specific membrane antigen)
  - membrane bound protein of the prostatic epithelial cell
- PAP (prostatic acid phosphatase)
  - phosphatase enzymes hydrolyze monophosphate esters → inorganic P + alcohol
  - also found in osteoclasts
- prostate specific protein 94,  $\beta$ -microseminoprotein,  $\beta$ -inhibin
- Zn<sub>2</sub> glycoprotein: fn is unknown
- leucine aminopeptidase: product of epithelial cells of prostate, decreased in prostate ca
- LDH: 4 subunits (MMMM, MMMH, MMHH, MHHH, or HHHH)
- Ig, C3, transferrin (increased in prostate ca)
- SV secretory proteins: semenogelin

### Where is PSA found outside of the prostate?

- breast tissue: malignant and normal
- breast milk
- female serum
- adrenal and renal carcinomas

### How is PSA processed?

- pre-pro-PSA processed in ER of prostatic epithelial cells
- pro-PSA is secreted and cleaved by hK2 to form active PSA

### What diseases can cause an increase in PAP?

- Paget's disease
- osteoporosis
- nonprostatic bone mets
- increased bone resorption
- metastatic prostate ca

### What is involved in the coagulation and liquefaction of semen?

- 5min after ejaculation: semen coagulates into semisolid gel → due to semenogelin
- 5-20min later: clot spontaneously liquefies to form a viscous liquid → due to PSA, plasminogen activators
- 1<sup>st</sup> fraction: primarily from Cowper's gland and prostate
  - contains liquefaction factors PSA and plasminogen activators (related to urokinase)
- final fraction: primarily from SV secretions
  - responsible for coagulation
- other proteolytic enzymes in semen: pepsinogen, lysozyme, amylase, and hyaluronidase
  - semen inhibits trypsin

### What drugs reach concentrations in prostatic secretions that approach or surpass concentration in blood?

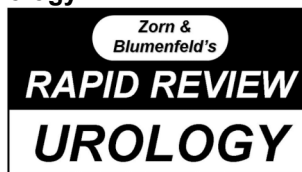
- macrolides: erythromycin and oleandomycin

### **Chapter 37 Questions - Prostate physiology.doc**

- sulfonamides
- chloramphenicol
- tetracycline
- clindamycin
- TMP
- quinolones
  - only EtOH, iodine, few antibiotics can enter semen by simple diffusion







### Chapter 38

## • Etiology, Pathophysiology, Epidemiology, and Natural Hx of BPH •

What factors contribute to the development of BPH?

|                                |   |
|--------------------------------|---|
| 1. Hyperplasia                 | ↓ apoptosis?  |
| 2. Endocrine                   | 1) Androgens<br>a) Regulation of apoptosis<br>b) Stromal-epithelial interaction |
| 3. Growth factors              | 2) Estrogens<br>1) Keratinocyte GF<br>2) Basic fibroblast GF<br>3) EGF          |
| 4. Prostate inflammatory cells | Growth factors  |
| 5. Genetic                     | AD  |

- hyperplasia
  - no clear evidence of an active proliferative process
  - increased # of epithelial and stromal cells in periurethral area of the prostate
  - aging process may cause decrease in overall rate of cell death
- androgens
  - development of BPH requires presence of testicular androgens during prostate development, puberty, and aging
    - pts castrated before puberty, or those w/ impaired androgen action/production → do not develop BPH
    - early imprinting of prostatic tissue by postnatal androgen (2-3mo surge) is critical to future hormonal induced growth
  - androgen withdrawal leads to partial involution of established BPH
  - prostate keeps high levels of AR throughout life: other organs (penis) lose AR and possibility for AR-dependent growth
  - DHT not increased in BPH
  - ?higher nuclear AR levels in BPH than in N prostate
- estrogen
  - estrogen levels increase in men w/ age
    - 2 forms of estrogen R:  $\alpha$  (made by stromal cells) and  $\beta$  (made by epithelial cells)
  - pts w/ larger volumes of BPH have higher estradiol levels
  - decreases in intraprostatic estrogen decrease drug-induced stromal hyperplasia: in animal models
- abnormalities in apoptosis: castration leads to active cell death in luminal epithelium and distal ducts
- stromal-epithelial interaction
  - one class of stromal cell excretory protein (ECM) regulates epithelial cell differentiation
  - BPH may be due to defect in stromal component that normally inhibits cellular proliferation
    - stroma may be causing epithelial cell development
- growth factors
  - 1<sup>st</sup> degree relatives have 4X increased risk of BPH
  - KGF, EGF, IGF, bFGF cause cellular proliferation
    - KGF is the leading candidate for the factor mediating
  - TGF- $\beta$  causes inhibition of proliferation in prostate → may be downregulated
- prostatic inflammatory cells
  - activated T cells may express growth factors: VEGF
- genetic and familial factors
  - AD inheritance pattern
  - 50% of men undergoing TURP for BPH if < 60 have familial risk (9% if > 60)
- PRL
  - transgenic mice overexpressing PRL have significant prostatic enlargement

## Chapter 38 Questions - BPH Epi.doccemiology

### What are the factors that cause the LUTS seen in BPH?

- Bladder outlet obstruction
  - prostate hyperplasia
  - non-BPH causes of obstruction
- Detrusor compensatory response
  - aging effects
  - neurogenic disease
  - primary bladder disease
- Polyuria

### What is the DDx for LUTS?

- Extra-genitourinary
  - mass compressing bladder
- Bladder
  - UTI (bacterial, viral, fungal, parasitic)
  - Neurogenic bladder
  - Dysfunctional voiding
  - Bladder ca and CIS
  - BN contracture
  - Bladder stone
  - IC
  - Malakoplakia
  - Foreign body
- Prostate
  - Prostate ca
  - Prostatitis (ABP, CBP, NBP)
  - BPH
  - Prostatic abscess
- Urethra
  - PUV
  - Urethral stricture
  - Urethral tumour
  - Obstructing urethral diverticulum
  - Urethritis
  - Meatal stenosis

**Transition zone** surrounds the urethra proximal to the ejaculatory ducts

**Central zone** surrounds the ejaculatory ducts and projects under the bladder base \*(different embryonic origination)

**Peripheral zone** constitutes the bulk of the apical, posterior, and lateral aspects of the prostate

**Anterior fibromuscular stroma** extends from the bladder neck to the striated urethral sphincter

### Where does BPH arise in the prostate?

- all BPH nodules develop in either the TZ or periurethral region
  - 2 separate glands in the TZ
    - main ducts of the TZ on lateral urethral wall near veru
    - periurethral zone glands proximal to origin of main TZ ducts

### What is the origin of the middle lobe in BPH?

- periurethral origin
  - no TZ tissue in this area

### What are the histologic features of BPH?

- true hyperplasia: increase in cell #
  - **hypertrophy is a misnomer**
- early periurethral nodules: stromal in character
- early TZ nodules: proliferation of glandular tissue
  - glandular nodules derived from newly formed small duct branches
  - form totally new ductal system in the nodule
- 2 phases of evolution:
  - 1<sup>st</sup> 20 years: increased # of nodules, growth of each nodule is slow
    - glandular nodules tend to be larger than stromal nodules
  - 2<sup>nd</sup> phase: size of individual nodules increase

What is the role of prostatic smooth muscle in BPH?

## Chapter 38 Questions - BPH Epi.docdemiology

- prostatic **smooth muscle represents significant volume** of the gland
- passive and active forces
  - passive: elastic elements in stromal and epithelial cells and **ECM (more important)**
  - active: stimulation of adrenergic R increases prostatic urethral resistance
    - $\alpha_{1A}$  receptor subtype is most abundant adrenoceptor in human prostate
    - endothelin R may also regulate

### How does androgen ablation affect cell populations in the prostate?

- **stromal cells resistant** to effects of androgen withdrawal
- affects epithelial cell population primarily

What is the bladder's response to obstruction?

- Clinical
  - obstruction-induced changes in bladder function
    - detrusor instability and decreased compliance → sx of frequency and urgency
    - decreased detrusor contractility (decompensation) → poor stream, hesitancy, intermittency, increased PVR
  - 1/3 of men have significant voiding dysfunction after surgical relief of obstruction
- Histologic
  - initial response of detrusor is development of smooth muscle hypertrophy → leads to detrusor instability
    - trabeculation: due to increase in detrusor collagen → leads to decreased compliance, increased PVR
  - changes in smooth muscle cell contractile protein expression, energy production, and cell-cell communication

### What is the definition of BPH?

- presence of stromal/glandular hyperplasia on surgical specimen

### What is the prevalence of BPH?

- autopsy studies: histology
  - no men < 30 have evidence of BPH
  - increases rapidly in 4<sup>th</sup> decade
  - 88-100% of men in 80s
- LUTS prevalence: **clear trend of increasing sx w/ advancing age**
  - 40-49: 18%
  - 50-59: 29%
  - 60-69: 40%
  - 70-79: 56%
- Bother, embarrassment, impact on QOL
  - **bother increases w/ advancing age → more important than frequency and severity**
  - QOL worse in men w/ higher sx frequency

### How can one classify sx severity in BPH?

- AUA symptom index: IPSS
  - 0-7 pts: mildly symptomatic
  - 8-19: moderate
  - 20-35: severe
- similar responses if self-administered, read to pt, mailed

### How does TRUS-determined prostate volume change w/ age?

- increases slowly but steadily w/ advancing age
- MRI gives prostate volumes 10% larger compared w/ TRUS
- TPV increases from approximately 25 to 35-45cc from age 30 → 70
- TZV increases from 15 to 25cc from 30 → 70 yrs

### What are the potential RF for developing BPH?

- +ve RF
  - **Age: most critical RF for developing BPH**
  - **Androgens: major RF**
    - presence of functioning testes at puberty
  - FHx/genetics
  - Medications
    - cold medications w/  $\alpha$ -sympathomimetic effects worsen LUTS
    - antidepressants, antihistamines, bronchodilators increase IPSS scores by 2-3 pts

## Chapter 38 Questions - BPH Epidemiology

- Obesity
  - +ve relationship b/w obesity, prostate volume, and LUTS
    - ◆ but, men w/ lower BMI have higher serum T levels
  - Type 2 DM, htn, obesity: may be RF
- Socioeconomic factors
  - increased income: higher rates of BPH
    - ◆ higher rates of surgery in lower income groups
  - education: affect expectations after treatment
- -ve RF
  - EtOH: lower prevalence of BPH in men w/ cirrhosis, due to decreased plasma T levels
- No role
  - Religion: Jews more likely to seek TURP, not more likely to get BPH
  - Sexual activity and vasectomy: no proven role
  - Hypertension: no proven association
  - Smoking: weak effect w/ little clinical significance: increases T and estrogen levels
  - Diet: no evidence of dietary factors to play a role

### Does IPSS score correlate w/ bother and QOL?

- strong correlation b/w IPSS, bother, and QOL

### How does volume correlate w/ sx severity?

- no correlation b/w sx, flow rate, and prostate volume
- no correlation b/w sx, Qmax, or volume and presence/degree of obstruction
- max flow rate decreases w/ increasing sx severity
- **stronger correlation may exist b/w TZ volume and sx and max flow rate**

### Correlations of measure of symptoms and BOO in pts with BPH

| Poor correlations                    |   |
|--------------------------------------|---|
| Sx severity and frequency (IPSS)     | Pressure-flow studies   |
| Bother                               |   |
| Interference                         |   |
| Disease-specific health-related QOLs |   |
| Maximum flow rate                    |   |
| Prostate volume                      |   |
| Prostate volume                      | IPSS  |
|                                      | PVR   |
| IPSS                                 | P-F studies   |
|                                      | - severe Sx, no obstruction in 22%  |
|                                      | - mild Sx, no obstruction in 100%   |
|                                      | - Hx/PE correctly identified subgroup with 80% probability of physiologic obstruction |
| Strong correlations                  |   |
| Sx severity and frequency (IPSS)     |   |
| Bother                               |   |
| Disease-specific health-related QOL  |   |
| Interference scores                  |   |
| Prostate volumes                     | ↓ peak and average flow   |

### What is the natural history of untreated BPH?

- Watchful waiting studies: 5 studies
  - Qmax deteriorated in 66%, improved in 20%
  - PVR increased, decreased, and stayed same in 1/3, 1/3, 1/3
- Wasson (1995): 556 men randomized to watchful waiting or TURP
  - 10% treatment failure (death, recurrent UTI, PVR > 350cc, bladder stone, UI, IPSS > 24, Cr doubling) in watchful waiting group, 5% in surgery group
  - most significant RF for predicting crossover from watchful waiting to surgery = **high baseline bother**
    - 25% men assigned to WW cross to surgery within 3yrs
- Placebo and sham control groups

## Chapter 38 Questions - BPH Epi.docdemiology

- short- to mid-term medical treatment
- 40% chance of improvement
- placebo-treated groups had improvements of IPSS score from 1.4-7.5pts
- PLESS (Proscar Long-term Efficacy and Safety Study)
  - 3000 men w/ moderate sx and enlarged glands
  - randomized to tx w/ finasteride 5mg vs. placebo for 4yrs
  - mean sx score and flow rate had initial placebo response, then drifted back to baseline
  - serum PSA found to predict rate of deterioration of bother and peak flow rate
- Longitudinal population based studies
  - Diokno (1992): 803 community dwelling men aged > 60
    - annual incidence of TURP: 2.6-3.3%
    - remission in 23%
  - Olmsted County data
    - increasing IPSS score of 0.34 per year, 31% men reporting 3pt increase
    - greatest increase for men in 60s, **0.6pt increase / yr**
    - decrease in flow rate of 2% / yr
    - increase in TRUS volume of 0.6cc / yr (6cc per 10yrs)

### What is the relationship b/w IPSS change and perception of improvement?

- Barry (1995) – dependent on baseline sx severity → takes change of 3 in IPSS to notice a difference in sx
  - marked improvement: -8.8
  - moderate improvement: -5.1
  - slightly improved: -3.0
  - unchanged: -0.7
  - **worse: + 2.7**

### What are the potential adverse outcomes from BPH?

- worsening of sx
- UI: due to overflow or detrusor instability
  - **detrusor instability in up to 50% of men w/ BOO**
- ED
- acute retention
  - etiology of AUR not known
  - overall incidence of 1-8%, 0-2% per year
  - 25-30% of men for TURP had AUR as main indication for OR
  - after *spontaneous AUR*, 15% men had another episode of AUR, and 75% required surgery
  - after *precipitated AUR*, 9% had another episode of AUR, and 26% required surgery
    - **much higher risk for recurrence or TURP after spontaneous AUR vs. precipitated**
- need for surgery
  - most pts undergo TURP for sx, not for AUR → TURP is softer endpoint for studies compared w/ AUR
- hematuria: 2.5% in BPH
  - finasteride reasonable 1<sup>st</sup>-line therapy: influences expression of VEGF
- UTI: main indication for TURP in 12%
- bladder stones: 8X increased risk → 3.4% in men w/ BPH, 0.4% in controls
- bladder diverticula
- detrusor failure: no direct evidence that delayed intervention may lead to progressive irreversible loss of bladder function
- upper tract deterioration/azotemia/renal failure: 14% of men presenting for TURP had evidence of CRF
  - 7.6% have hydro, 1/3 of whom have renal insufficiency
- death

### What is meant by precipitated AUR?

- inability to urinate after a triggering event
  - non-prostate related OR, catheterization, anaesthesia, sympathomimetic/anticholinergic medication

### What are the RF for developing AUR in BPH?

- age
- baseline sx severity
- presence of LUTS: incomplete emptying, frequency, weak stream best independent predictors
- use of anticholinergics or  $\alpha$ -agonists
- elevated PSA

## Chapter 38 Questions - BPH Epi.docdemiology

- 5.6-7.7% for men w/ PSA < 1.4
- 7.8-10.2% for men w/ PSA > 1.4

### What are the RF for requiring TURP in BPH?

- BLSA study
  - age
  - incomplete emptying
  - change in stream
  - BPH based on DRE
- 0 RF 3%, 1 RF 9%, 2 RF 16%, 3 RF 37%

### What is the probability of undergoing surgery based on sx severity?

- Barry (1997)
  - mild: 10%
  - moderate: 25%
  - severe: 40%

### What is the DDX of urinary retention?

- Bladder failure
  - Underlying causes
    - atonic bladder
      - ◆ brain: stroke, Parkinson's, HI, tumour, MS
      - ◆ cord: SCI, MS, tumour, spina bifida, tethered cord, SC compression, cauda equina
      - ◆ peripheral nerves: DM, EtOH, CRF, surgical (APR, RP)
  - Exacerbated by
    - UTI
    - bladder overdistention with myogenic failure
    - drugs:
      - ◆ anticholinergics (Atropine, Ditropan)
      - ◆ narcotics (morphine)
      - ◆ antihistamines
      - ◆ antidepressants (TCAs)
      - ◆ antipsychotics
      - ◆ alpha-adrenergic agonists (Sudafed, Ornade)
    - constipation
    - pain
    - immobilization
    - residual anesthetic
    - large diuresis (EtOH, diuretics)
    - prostatic infarction
- Obstruction
  - Bladder
    - tumour
    - clot retention
    - foreign body
    - bladder stone
    - edema from UTI
    - cystocele
    - ureterocele
    - diverticula
    - BN contracture
  - Prostate
    - BPH
    - prostate cancer
    - prostatitis
  - Pelvic Floor
    - spasm from pain
    - DSD
  - Urethra
    - stricture

### **Chapter 38 Questions - BPH Epi.docdemiology**

- tumour
- foreign body
- stone
- meatal stenosis
- phimosis







## Chapter 39

### • Evaluation and Non-surgical Management of BPH •

#### What is meant by the following terms:

- microscopic BPH: histologic evidence of cellular proliferation of the prostate
  - proliferative process of stromal and epithelial elements of prostate
  - originates in TZ and periurethral glands
- macroscopic BPH: enlargement of prostate from microscopic BPH
  - strong correlation b/w PSA and prostate volume
  - TZ accounts for majority of BPH tissue
- clinical BPH: LUTS, bladder dysfunction, hematuria, and UTI from macroscopic BPH

#### What is involved in the evaluation of a pts w/ LUTS?

- Hx
  - GU hx: strictures, AUR, previous TUR, STDs, prostatitis
  - LUTS, polyuria
  - complications of BPH: stones, hematuria, UTI, diverticuli, AUR, renal failure, aggravation of sx by cold meds
  - previous tx for BPH
  - PMHx: DM, CNS disease (Parkinson's, stroke), general health
  - Meds: anticholinergics,  $\alpha$ -agonists
  - **IPSS: sx score is primary determinant of tx response**
    - to pts, relief of sx is single most important outcome
- Px
  - BP: htn, risk of CRF
  - body habitus: feasibility for OR
  - DRE: prostate size, consistency, tenderness, nodules, rectal ca
  - focused neurologic exam, anal tone
  - external genitalia: meatal stenosis, urethral mass
  - abdo exam: palpable bladder
- U/A, urine C&S: r/o UTI, hematuria
- cytology: in men w/ severe irritable sx
- Labs
  - Cr (optional by 5<sup>th</sup> International consultation on BPH), lytes, CBC → not recommended in 2003 AUA guidelines
    - 13.6% pts have renal insufficiency: increased risk for post-op complications
    - elevated Cr is indication for upper tract imaging (abdo US)
  - **PSA → perform in men in whom the dx of prostate cancer would change management**
    - 28% of men w/ histologically proven BPH have PSA > 4
- Additional testing
  - no further testing needed in pts w/ absolute indications for TURP (SHITRR) unless suspect AUR due to bladder disease
  - Cysto
    - **not recommended to determine need for tx**
    - perform in men if invasive tx is considered (McConnell 1994), or hx of: hematuria, stricture, ca, previous TURP
      - ◆ useful to determine feasibility of specific therapy: TUIP vs. TURP vs. open simple
    - minimal correlation b/w endoscopic appearance of lower tract and treatment outcome
      - ◆ trabeculation may predict slightly higher failure rate in pts w/ watchful waiting
  - UDS
    - uroflow
      - ◆ volume must be > 150cc, Qmax better than Qave
      - ◆ Qmax decreases w/ age and voided volume
      - ◆ Qmax can predict response to TURP
        - ◆ pts w/ Qmax > 15cc/sec have poorer treatment outcomes than pts w/ Qmax < 15cc/sec
      - ◆ low Qmax cannot differentiate b/w detrusor weakness vs. BOO

## Chapter 39 Questions - BPH Eval+Tx.doc

- PVR
  - ◆ normal PVR 0.09-2.24cc (mean 0.53cc)
  - ◆ PVR does not correlate w/ LUTS, UDS, or flowrate
  - ◆ **no specific PVR threshold exists → use only as "safety parameter"**
  - ◆ uncertain if increased PVR predicts response after TURP, or impending renal or bladder damage
- pressure-flow studies
  - ◆ indicated if initial evaluation, Qmax, and PVR are not sufficiently suggestive of BOO, considering TURP, if surgical tx has failed, hx neurologic disease,
  - ◆ differentiates b/w low Qmax from obstruction vs. decompensated bladder
  - ◆ value in predicting tx outcome is uncertain
- CMG + video UDS
  - ◆ adds limited information: not recommended in routine cases
  - ◆ useful in men w/ known/suspected neurologic lesions and LUTS
- Imaging
  - not recommended for routine evaluation of men w/ LUTS
  - Indications for upper tract imaging in men w/ LUTS: hematuria, UTI, renal failure, hx stones, hx, GU surgery
  - renal imaging normal in 75%
  - most recommend US + KUB → will dx most abnormalities

### Recommendations Of The International Scientific Committee:

#### Evaluation and Treatment of LUTS suggesting benign prostatic obstruction

|   |   |
|---|---|
| <b>Highly recommended</b><br>(all patients)   | <ol style="list-style-type: none"> <li>1. History (quantification of symptoms and quality of life)</li> <li>2. Physical exam and DRE</li> <li>3. Urinalysis (Dipstick)</li> </ol>                       |
| <b>Recommended</b><br>(valuable, strongly encouraged)                                       | <ol style="list-style-type: none"> <li>1. Voiding diary (frequency and volume chart)</li> <li>2. Cr</li> <li>3. PSA</li> <li>4. Uroflow</li> <li>5. PVR</li> </ol>                                      |
| <b>Optional</b><br>(proven useful in selected patients)                                     | <ol style="list-style-type: none"> <li>1. Pressure-flow (proven value for selected pts)</li> <li>2. Upper tract imaging (US or IVP)</li> <li>3. Prostate US (TRUS or TAUS)</li> <li>4. Cysto</li> </ol> |
| <b>Not recommended</b><br>(will not help evaluate most pts but useful in selected patients) | <ol style="list-style-type: none"> <li>1. UPP</li> <li>2. Filling CMG</li> <li>3. RUG</li> <li>4. VCUG of the external urinary sphincter</li> </ol>   |

### What are the indications for surgery in men w/ BPH?

- Absolute:
  - Bladder Stones
  - Hematuria
  - recurrent Infections
  - large diverticulae
  - Renal failure
  - urinary Retention
- Relative
  - pt prefers TURP
  - sx affecting QOL (generally IPSS 8 or more)
  - failure of medical therapy (due to s/e or lack of efficacy)
  - impaired bladder emptying (high PVR)
  - ?low Qmax from BOO

### What are the indications for cysto in men w/ LUTS?

- hx of micro/gross hematuria
- hx of strictures (or at risk for strictures: urethritis, urethral injury)
- hx of bladder ca or +ve cytology
- hx of prior lower tract surgery: TURP
- men w/ moderate/severe LUTS pre-surgery: planning surgical therapy

## Chapter 39 Questions - BPH Eval+Tx.doc

### What are the benefits of cysto in men w/ BPH?

- ability to demonstrate BPH and visual obstruction of urethra and BN
- identify specific anatomic abnormalities
- identify bladder stones, trabeculation, cellules, diverticula
- measure PVR
- r/o unrelated bladder and urethral pathologic processes

### What are the goals of treatment for BPH?

- relieve LUTS
- decrease BOO
- improve bladder emptying
- improve detrusor instability
- reverse renal failure
- prevent future episodes of hematuria, UTI, and AUR

### What outcome measures can be used to measure response to treatment for BPH?

- Symptoms
- BOO
  - **sx severity not related to degree of BOO**
  - Nitti (1994): pts w/ BPH classified as obstructed, equivocal, and unobstructed (on AG nomogram) have same mean AUA score
- Bladder emptying: clinical significance is controversial: no data shows if incidence of UTI related to PVR
  - decreased chance of successful voiding if bladder volume > 900cc
- Detrusor instability
  - historically defined as detrusor contraction > 15cm H<sub>2</sub>O at bladder volume < 300cc
    - any involuntary increase in Pdet associated w/ urgency qualifies as instability (Nitti 1998)
  - presence of **detrusor instability does not predict response** to treatment
- AUR: likelihood of successful TOV related to bladder volume at time of initial bladder drainage
- UTI: no evidence that UTI associated w/ PVR or BOO
- Renal failure
- Hematuria

### How can one select appropriate pts w/ BPH for medical therapy?

- sx should be bothersome and –vely affect QOL
  - high sx score not enough: need bother
- should be no absolute indications for TURP

### What are the potential options for nonsurgical management of BPH?

- **pts w/ absolute indications for surgery should not be offered medical therapy**
  - **can develop life-threatening complications**
- watchful waiting
- behavioural modification: BEHAVE (bladder retraining, education, habits, prompted voiding, voiding diary, exercises)
- $\alpha$ -blockers
- anticholinergics and musculotropics: for minimal obstruction + DI
  - Propantheline (Pro-Banthine), Hyoscamine (Levsin), Oxybutinin (Ditropan), Dicyclomine (Bentylol), Flavoxate (Urispas), Tolteridine (Detrol)
- TCA: imipramine (Tofranil), doxepin (Sinequan)
- androgen suppression
- combination therapy
- aromatase inhibitors
- phytotherapy
- circumventing the problem: CIC, indwelling, SP

### What is involved in conservative tx of BPH?

- decrease total fluid intake, esp before bedtime
- limit EtOH, caffeine, carbonated beverages
- timed voiding
  - treatment failure in 17%

## Chapter 39 Questions - BPH Eval+Tx.doc

### What are the different subtypes of the $\alpha_1$ -receptor?

- $\alpha_{1A}$  – predominant in human prostate stroma  
→ mediates prostate smooth muscle tension
- $\alpha_{1B}$  – predominate in human prostate epithelium
- $\alpha_{1D}$
- ( $\alpha_{1L}$  – in prostatic stroma, may be conformational state of 1A)

### How can one classify $\alpha$ -blockers?

- Nonselective  
→ Phenoxybenzamine (Dibenzylamine) 10mg PO BID → irreversible  
➢ efficacy of phenoxybenzamine and prazosin comparable, but prazosin better tolerated
- $\alpha_1$   
→ Prazosin (Minipress) 2mg PO BID  
→ Alfusosin IR (Xatral) 2.5mg PO TID  
→ Indoramin 20mg PO BID
- Long-acting  $\alpha_1$   
→ Terazosin (Hytrin) 5-10mg PO OD  
➢  $t_{1/2}$  12hrs  
➢ dose-dependent improvements in sx scores by 4pts below placebo  
➢ adverse events: postural hypotension, asthenia, flu sx, dizziness, syncope, peripheral edema  
◆ give 1<sup>st</sup> dose as 1mg and in pm to prevent "first dose effect"  
➢ durable clinical response, maximal improvement after 3 months of use  
➢ improves peak flow rate by 2-3cc/sec  
➢ change in BP: small and insignificant if normotensive, larger and significant if hypertensive  
→ Doxazosin (Cardura) 4-8mg PO OD  
➢  $t_{1/2}$  22 hrs → longer than Hytrin  
➢ no renal adjustment necessary, use w/ caution in hepatic insufficiency  
➢ dose dependent improvement in sx score by 2-5pts, improves PFR by 1.5-3.5cc/sec → similar to Hytrin  
➢ BP changes greater compared w/ Hytrin  
→ Alfusosin SR 10mg PO OD  
➢ improvement in sx score by 1-2pts, improves PFR by 1-1.5cc/sec  
➢ no significant change in BP, no dizziness/asthenia, no sexual dysfunction  
◆ better tolerated → may be due to lower level of blockade
- Subtype selective  
→ Tamsulosin (Flomax) 0.4mg PO OD  
➢ most potent  $\alpha_1$  blocker  
➢ some modest specificity for  $\alpha_{1A}$  receptor  
➢ sx score improvements higher for 0.8mg vs. 0.4mg  
➢ adverse effects: dizziness (5%), asthenia (3%), rhinitis (3%), abnormal ejaculation (6%): 6%, 3%, 9%, 18% in 0.8mg  
➢ 0.4mg felt to be the only reasonable dose, due to s/e and cost of 0.8mg

### How does $\alpha$ -blockade affect success of TOV?

- McNeill (1999)  
→ alfuzosin 5mg PO BID vs placebo in men w/ AUR, foley removed for TOV 24h after treatment  
➢ excluded if PVR > 1500cc  
→ 55% of treated vs. 29% of placebo pts voided spontaneously after cath removal

### What adverse events of alpha blockade are particularly troublesome in the elderly?

- dizziness and orthostatic hypotension: leads to increased episodes of falls
- incidence of **adverse events are not age dependent**

### How does $\alpha$ -blockade affect pts w/ htn?

- terazosin and doxazosin lower BP in hypertensive men to significant degree: doxazosin more
- 30% of men treated for BPH have htn

### What is the mechanism of adverse effects associated w/ $\alpha$ -blockade?

- dizziness and asthenia most common s/e → likely due to effects at level of CNS  
→ not due to changes in BP as previously assumed

## Chapter 39 Questions - BPH Eval+Tx.doc

### How does androgen suppression treat BPH?

- embryonic development of the prostate dependent on DHT
- BPH is an androgen dependent process
- androgen suppression causes regression primarily of the epithelial elements of the prostate  
→ but, clinical BPH sx not dependent on prostate size
- takes 6 months, may only work in men w/ large prostates

### How do the different $\alpha$ -blockers compare?

- alfuzosin IR vs. tamsulosin: no difference in dizziness, asthenia, BP changes
- terazosin vs. doxazosin: comparable effectiveness and tolerability
- tamsulosin 0.4mg less effective than terazosin 10mg and doxazosin 8mg, no better tolerance  
→ advantage only is no need for dose titration, decreased time to TOV

### Comparison of the commonly used alpha blockers

|                   | Onset                               | Side effects   | Special considerations  |
|-------------------|-------------------------------------|--|---|
| <b>Terazosin</b>  | 2 weeks                             | <ol style="list-style-type: none"> <li>1. somnolence</li> <li>2. asthenia</li> <li>3. postural hypotension 5%</li> <li>4. syncope 1%</li> <li>5. dizziness</li> <li>6. <b>nasal congestion</b></li> <li>7. <b>impotence</b></li> <li>8. ↓ cholesterol</li> <li>9. priapism</li> </ol>                | <ul style="list-style-type: none"> <li>- 1<sup>st</sup> dose effect at 3 hours</li> <li>- PM dosing, start w/ 1 mg</li> <li>- interaction with verapamil (Isoptin®)</li> <li>- Irritative sx improvement at 10 mg; obstructive sx at 5 mg; total sx at 10 mg; flow ↑ at all doses</li> <li>- Postural hypotension sig at 5 mg</li> <li>- special indication: hypertensive men</li> </ul>  |
| <b>Doxazosin</b>  | 1 week                              | <ol style="list-style-type: none"> <li>1. somnolence</li> <li>2. asthenia</li> <li>3. <b>hypotension &gt; terazosin</b></li> <li>4. <b>syncope 0.5%</b></li> <li>5. dizziness</li> <li>6. <b>headache</b></li> <li>7. <b>nausea</b></li> <li>8. ↓ cholesterol</li> <li>9. priapism (rare)</li> </ol> | <ul style="list-style-type: none"> <li>- 1<sup>st</sup> dose effect at 2-6 hours (check BP routinely)</li> <li>- AM or PM dosing (?why)</li> <li>- Sig sx improvement at 4 and 8 mg only (vs. PFR improvement at all doses)</li> <li>- special indication: hypertensive men</li> </ul>  |
| <b>Tamsulosin</b> | adjust dose at 2-4 weeks<br>? onset | <ol style="list-style-type: none"> <li>1. dizziness 3%</li> <li>2. abnormal ejaculation 3% <ul style="list-style-type: none"> <li>- retrograde</li> <li>- ↓ volume</li> </ul> </li> <li>3. headache 2%</li> </ol>  | <ul style="list-style-type: none"> <li>- Fasting results in 30% ↑ in bioavailability and 40-70% ↑ in peak concentration</li> <li>- Postural hypotension, syncope and tachycardia 1% for both placebo and treatment</li> <li>- Night time dosing and post-dose blood pressure monitoring is not necessary</li> <li>- special indication: acute urinary retention, pts at risk of hypotension, pts who don't tolerate terazosin/doxazosin at 10/8 mg</li> </ul> |

### How can one classify meds for androgen suppression?

- Central
  - LHRH agonists
    - leuprolide (Lupron or Eligard) 22.5mg IM q3mo
    - buserelin (Suprefact)
    - goserelin (Zoladex) 10.8mg SC q3mo
    - nafarelin (Synarel) 400mg SQ OD
  - LHRH antagonist
    - cetorelix (Cetrotide) 1mg SQ OD – LHRH analogue
      - ◆ possible to titrate level of androgen suppression
      - ◆ improves sx score, PFR, prostate volume
  - estrogens: DES, PES
  - progestational agents
    - 17 $\alpha$ -hydroxycortisone 200mg IM qweek
    - megestrol acetate (Megace) 40-250mg PO TID: synthetic derivative of progesterone
- Peripheral

## Chapter 39 Questions - BPH Eval+Tx.doc

- antiandrogens
  - steroidal
    - ◆ *cyproterone* (Cyprostat)
    - ◆ *zanoterone* 100-800mg PO OD
      - ◆ competitive AR blocker, poor efficacy for BPH
      - ◆ high incidence of s/e: breast pain (56%), gynecomastia (22%)
  - nonsteroidal (pure)
    - ◆ *flutamide* (Chimax, Drogenil) 100-250mg PO TID
      - ◆ poor efficacy, no difference w/ placebo
    - ◆ *nilutamide* (Anandron)
    - ◆ *bicalutamide* (Casodex) 50mg PO TID
- Inhibitors of steroid synthesis
  - ketoconazole
  - spironolactone
  - adrenolytic drugs: metapyrone, aminoglutethamide, mitotane (ortho-para-DDD)
  - 5 $\alpha$ -reductase inhibitors
    - *epristeride*: dual inhibitor of 5 $\alpha$ -reductase
    - *finasteride* (Proscar) 5mg PO OD
      - ◆ no renal dose adjustment, use w/ caution in hepatic insufficiency (metabolized by P450)
      - ◆ s/e: sexual dysfunction (decreased libido, ED, decreased ejaculatory volume), breast enlargement and tenderness, rash
      - ◆ North American Finasteride Trial: 895 men w/ BPH received placebo, 1mg, or 5mg of finasteride
        - ◆ changes in sx score: -2%, 9%, 21%, changes in PFR: 8%, 23%, 22%, volume change: -3%, -18%, -19%
        - ◆ s/e: decreased libido, ejaculatory d/o, ED → 2-4%
      - ◆ Proscar Long-Term Efficacy and Safety Study (PLESS): 3040 men w/ LUTS got placebo vs. 5mg finasteride x 4y
        - ◆ baseline prostate volume 55cc
        - ◆ sx and PFR improvement modest, consistent w/ previous trials
        - ◆ decreased risk of AUR (3% vs. 7%) and undergoing TURP (5% vs 10%)
        - ◆ no change in detection of prostate cancer
        - ◆ PdetQmax 115 vs 126cmH<sub>2</sub>O: both groups severely obstructed before and after treatment
      - ◆ finasteride very effective in treating post-TURP hematuria
    - *dutasteride* (Avodart) 0.5mg PO OD
- Combined androgen blockade (MAB)
  - LHRH + antiandrogen
  - castration + antiandrogen
- Alternative
  - PC-SPES

### What is the role of finasteride in clinical treatment of BPH?

- use in men w/ large prostates
  - decreases risk of AUR
- contraindications to  $\alpha$ -blockers
- gross hematuria
- dual therapy

### What is the role of aromatase inhibitors for BPH?

- estrogens may be involved in pathogenesis of BPH
- estrogenic effect mediates stromal-epithelial interactions that regulate proliferative activity of the prostate
- *atamestane* 400mg: decreases estradiol, estrone, T levels
  - **no change in sx score, PFR, or volume → do not use**

### What is phytotherapy?

- products from extracts of roots, seeds, bark, or fruits of various plants
  - *Serenoa repens* (saw palmetto) 160mg PO BID
    - many placebo-controlled studies published, but all are flawed: small #, short duration, lack of standardized sx scores
    - efficacy yet to be determined
  - *Hypoxis rooperi* (South african star grass) 20mg PO TID (Harzol)

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- *Pygeum africanum* (African plum tree) 50mg PO BID
- *Urtica dioica* (Stinging nettle)
- *Secale cereale* (Rye pollen)
- *Cucurbita pepo* (Pumpkin seed)
- *Opuntia* (Cactus flower)
- *Pinus* (Pine flower)
- *Picea* (Spruce)

#### What are the possible mechanisms of action of plant extracts?

- inhibition of 5 $\alpha$ -reductase
- anti-inflammatory
  - plant flavonoids are inhibitors of CO and lipoxygenase enzymes, decreasing PG synthesis
- interference w/ growth factors
- antiandrogenic
- estrogenic
- aromatase inhibition
- decrease of SHBG
- alteration of cholesterol metabolism
- action on  $\alpha$ -adrenergic receptors
- free radical scavenger
- alteration of lipid peroxidation
- modulation of PRL-induced prostatic growth
- protection of bladder and detrusor function
- placebo effect

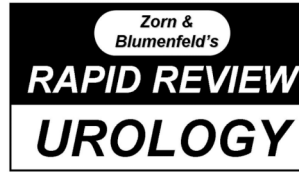
#### What are the AUA Guidelines for the management of BPH?

- Initial Evaluation
  - Hx: identify other causes of voiding dysfunction
  - Px: including DRE and focused neurologic evaluation
  - Labs: urinalysis + microscopy, PSA (cytology optional)
    - routine Cr not recommended
  - AUA sx index
  - uroflow + PVR: in pts w/ complex medical hx or those desiring invasive tx
  - Optional dx tests for pts that choose invasive therapy
    - PFR, cysto, U/S abdo, TRUS: optional in pts that choose invasive therapies or if prostate size important to consider tx
    - CMG, U/S kidneys: only if pt has hematuria, UTI, renal insufficiency, or hx stones or urinary tract surgery
- Treatment
  - Mild sx (AUA score < 8 or not bothered by more severe sx): watchful waiting
  - Moderate/severe sx (AUA score 8 or higher): explain benefit and harm of BPH tx options
    - Watchful waiting
    - Medical therapy
      - ◆ Alpha blockers: alfuzosin, doxazosin, tamsulosin, terazosin → for pts w/ LUTS due to BPH
        - ◆ prazosin, phenoxylbenzamine: not recommended
      - ◆ 5-alpha reductase inhibitors: dutasteride, finasteride
        - ◆ for pts w/ symptomatic prostatic enlargement but no bother, to prevent disease progression
        - ◆ not for pts w/o evidence of prostatic enlargement
      - ◆ Combination therapy
        - ◆ for pts w/ LUTS associated w/ prostatic enlargement
    - Minimally invasive therapy
      - ◆ TUMT: Prostatron, Targis, TherMatrx, CoreTherm → all equivalent
        - ◆ ensure pt has no radiation: increased risk of fistula
      - ◆ TUNA
      - ◆ Stents: UroLume → use only in high risk pts (due to high complication rate)
    - Surgery
      - ◆ TURP, TUVP, TUIP, HoLEP, TULVP, VLAP
      - ◆ open prostatectomy
  - Indications for surgery: bladder stones, persistent gross hematuria, recurrent UTIs, renal failure, retention (failure of TOV on alpha blocker)



### **Chapter 39 Questions - BPH Eval+Tx.doc**

- diverticulum: not an absolute indication for OR, unless associated w/ recurrent UTI or progressive bladder dysfunction
- New therapies: not recommended outside of research protocols
  - phytotherapies, interstitial laser therapy, HIFU, EtOH injection, water induced thermal therapies
  - balloon dilation: not recommended at all for BPH



## Chapter 40

### • Minimally Invasive and Endoscopic Management of BPH •

#### What are the options for surgical management of BPH?

- Minimally invasive
  - Stents
  - Transurethral needle ablation of the prostate (TUNA)
  - Transurethral microwave thermotherapy (TUMT) or hyperthermia
  - Laser prostatectomy
    - Transurethral laser-induced prostatectomy (TULIP)
    - Visual laser ablation of the prostate (VLAP)
    - Interstitial laser therapy (similar to TUNA)
    - Holmium laser resection of the prostate (HoLRP)
  - Electrosurgical prostatectomy
    - Transurethral incision of the prostate (TUIP)
    - Transurethral vaporization of the prostate (TUVF)
    - Transurethral resection of the prostate (TURP)
  - High intensity focused ultrasound (HIFU)
- Open
  - Simple open prostatectomy (retropubic, suprapubic or perineal)

#### What are the indications for permanent stenting?

- complex or recurrent urethral stricture disease
- DSD
- post-brachy BOO
- anastomotic strictures and UI after RP
- poor operative candidate w/ AUR

#### How can one classify the different types of stents that can be used for BPH?

- Temporary stents: nonabsorbable or biodegradable
  - neither become covered by urethral epithelium or become incorporated into urethral wall
  - removed q6-36mo: designed for short-term use
  - do not require GA, success in 50-90%
  - different types:
    - spiral stents:
      - ◆ should be used as nontraumatic therapy for retention in pts unfit for OR
      - ◆ 1<sup>st</sup> generation: Urospiral and ProstaKath
        - ◆ stainless steel, +/- gold plating to prevent encrustation, used for 12mo
        - ◆ high rate of complications: hematuria, migration, infection
      - ◆ 2<sup>nd</sup> generation: MemoKath and ProstaKoil
        - ◆ nickel-titanium alloys (nitinol), heat expandable (MemoKath) or self-expanding (ProstaKoil)
        - ◆ can be used for 36mo
    - polyurethane stents (aka intraurethral catheters)
      - ◆ intraurethral catheter: 16F, use for 6mo → proximal end like Malecot
      - ◆ Barnes stent: polyurethane, 16F
      - ◆ Trestle stent: tube in prostate + thread in external sphincter + tube in bulbar urethra
    - biodegradable stents: polyglycolic acid stent
- Permanent stents
  - UroLume
    - woven tubular mesh, gradually epithelialization occurs
    - s/e: epithelial hyperplasia, migration, LUTS, painful ejaculation → seen in 2<sup>nd</sup> generation stent
  - Memotherm
    - heat-expandable stent of nickel-titanium alloy, expands to flexible cylinder

## Chapter 40 Questions - TURP.doc

- complications high: migration, removal of stent, UTI, LUTS, stricture, urothelial hyperplasia, retreatment
- ASI stent: withdrawn
- Ultraflex stent

### What are the complications of intraprostatic stents?

- encrustation/stones, migration, breakage, SUI, bacteriuria, hematuria, pain, stricture, retreatment

### How does TUNA work?

- increase prostatic temperature to  $> 60^{\circ}\text{C}$
- use low-level radiofrequency (RF) energy via needles in prostate → produces localized necrotic lesions in hyperplastic tissue
- monopolar RF signal of 490 kHz produced in generator, connected to TUNA catheter
  - RF produces molecular or ionic agitation w/ collision of particles that relates to frequency of energy
- TUNA catheter can show needles entering prostate, needles sit within Teflon shield to protect urothelium
- tissue heating created due to tissue resistance to current
  - if power too high, prostate desiccates and chars rapidly w/ rise in tissue resistance → prevents desired heating effect
  - heat generated proportional to  $1/4^{\text{th}}$  power of radius
- active electrode has small surface area, RF concentrated in small area around it
  - return electrode large (grounding pad on sacrum), so diffusion of RF current return is greater
  - heat concentrated near active electrode only, need 5-7min
- delivered under local

### What are the lesions produced from TUNA?

- creates 1cm necrotic lesions w/o difficulty in prostate w/o damage to rectum, bladder base, or distal prostatic urethra
- lesion 1<sup>st</sup> appears as hemorrhagic lesion, max necrosis at 7d, fibrosis occurs by 15d
- NOS receptor damage occurs earliest, w/ damage to adrenergic R at 1-2 weeks

### Describe the technique of TUNA.

- lithotomy, Xylocaine jelly
- prophylactic antibiotic
- TUNA catheter advanced under vision w/ 0-degree scope
- exact position of needle tip in prostate visualized by TRUS
  - tip of needle should not lie within 5-6mm of outer rim of prostate
- Teflon shield advanced over proximal portion of needle
  - urethra protected by shield that extends from 5-6mm from TUNA catheter
- RF power set to 2-15W, 5 min per lesion
  - 2 lesions created each time power turned on
  - 1 pair of lesions treats 20g of prostate
  - 1 pair of lesions used for  $< 3\text{cm}$  of prostatic urethral length, 2 pair for 3-4cm, on extra plane for each 1cm extra
- procedure repeated for opposite lobe
- urethral temp kept  $< 46^{\circ}\text{C}$
- Foley x 1d

### What are the clinical results from TUNA?

- 8 studies:
  - decrease in sx score from 20-25 → 6-12 (average decrease by 13.1 units, or 58%)
  - increase in PFR from 3-10 → 10-17 (average increase in flow of 6cc/sec, or 77%)
- comparing TUNA to TURP
  - sx score decreases by 15 units in TURP (vs. 13.6 in TUNA)
  - PFR increases by 12.4cc/sec in TURP (vs. 6cc/sec in TUNA)
- 4 P-F studies
  - PdetQmax decreases from average 85cmH<sub>2</sub>O → 65cmH<sub>2</sub>O by 3mo (average decrease by 20%)

### What are the adverse effects seen w/ TUNA?

- low complication rate overall
  - post-tx urinary retention (13-42%) → most common complication
  - LUTS: 40% in early period after tx, but usually mild and last only 1-7d
  - bleeding (33%): mild, short-lasting → stop ASA prior to procedure
  - UTI (3-8%), stricture (1.5%)
- **no adverse effect of any kind on sexual function**

## Chapter 40 Questions - TURP.doc

- **no report of UI post-TUNA**
- need for re-operation in 12-14%, occurring < 2y postop

### What are the indications and contraindications for TUNA?

- lateral lobe enlargement and prostate size of 60g or less
  - pts w/ larger prostates, purely BN hypertrophy, or median lobe enlargements are not ideal candidates

### How does TUMT work?

- number of different theories:
  - heat changes and differential blood flow in prostate
    - cooling fluid in catheter: maintains urethral temp < 44°C
    - temperatures in prostate up to 70°C
    - tissue exposed to 45°C for 60min suffers hemorrhagic necrosis
    - sharp border b/w viable and necrotic tissue
    - low level of blood flow at rest, as heat energy delivered, blood flow increases
  - sympathetic nerve degeneration
    - microabscesses, epithelial necrosis, and vasculitis seen post-op
    - nerve fibers disrupted, axons rarely seen → ?thermal damage to adrenergic fibers
    - decrease in  $\alpha_1$ -adrenoceptor density after TUMT
  - induction of apoptosis
    - area of tissue damage seen after TUMT small in relation to overall prostate volume
    - moderate heat for longer period found to be best way to induce apoptosis
- 2 most commonly used machines: Prostatron and Targis

### What are the clinical results after TUMT?

- **machines delivering higher power have better results than lower power**
  - Low-energy software (Prostasoft 2.0)
    - sx score improves from mean of 14-16 → 5-7
    - PFR improves from 8.5 cc/sec → 11.3 cc/sec (increase by ~2-3cc/sec)
    - satisfaction rate of 62% at 1yr, 34% at 2yrs, 23% at 4 yrs → 66% require retreatment
    - no change in PdetQmax by 6mo
  - High-energy software (Prostasoft 3.5)
    - sx score decreases from 20 → 9
    - PFR improves from 9.5cc/sec → 14.5cc/sec
    - PdetQmax decreased from 59cmH<sub>2</sub>O → 47cmH<sub>2</sub>O
- TUMT vs. shams: improved PFR and IPSS vs. sham
  - PFR improved from 7.5-8.5 → 9.2-9.4 in sham, 7.2-8.5 → 11.5-13 in TUMT
  - sx score decreased from 14 → 13 in sham, 14 → 4-6 in TUMT
- neo-adjuvant and adjuvant use of  $\alpha$ -blockers seen to improve early results
- TUMT vs. TURP: **better flow after TURP, decreased complications w/ TUMT**
  - sx score decreases by 12 pts in TURP (9 pts in TUMT)
  - PFR increases by 10cc/sec in TURP (4cc/sec in TUMT)
  - greater complication rate in TURP: 25% retrograde ejaculation, 7.5% stricture rate
  - decrease in outflow obstruction greater after TURP than TUMT
  - need for catheter (CIC or indwelling) greater after TUMT
  - improvement in QOL greater w/ TURP

### What are the adverse effects after TUMT?

- retention
  - 36% require catheterization post-op, most for <1 week
- need for retreatment: 66%
- no retrograde ejaculation seen in TUMT
- no urethral stricture seen

### What different types of laser can be used to treat the prostate?

- Nd:YAG (Neodymium:Yttrium-Aluminum-Garnet)
  - light emitted at 1064nm, w/ neodymium atoms in yttrium-aluminum-garnet rod
  - light poorly absorbed by water and body pigments → penetrates deeply
  - causes thermal coagulation of surface tissue and areas below surface
  - total hemostasis

## Chapter 40 Questions - TURP.doc

- coagulated tissue sloughs over few weeks, up to 3mo for healing
- KTP (Potassium Titanyl Phosphate)
  - uses KTP crystal to double frequency of Nd:YAG laser
  - 532nm wavelength → intermediate level of coagulation and vaporization
  - only ½ tissue penetration vs. Nd:YAG, but higher energy per tissue volume → increases tissue vaporization and desiccation
  - can incise BN
- Ho:YAG (Holmium:Yttrium-Aluminum-Garnet)
  - 2100nm, emitted in series of rapid pulses over few millisec
  - produces cutting effect by vaporization of tissue water → causes less hemostasis
- Diode laser
  - more efficient use of photons generated → smaller machines

### How do lasers work?

- Light Amplification by Stimulated Emission of Radiation
  - flashlamp gives out high intensity light → bombards a resonator cavity w/ photons
  - photons excite electrons in the resonator cavity to higher energy status
  - excited orbitals are unstable, and rapidly decay, emitting a photon of defined wavelength
  - photons leave resonator cavity as a coherent laser beam

| Advantages of laser therapy   | Disadvantages of laser therapy  |
|---|---|
| 1. No bleeding or transfusion   | 1. New – less long-term data than TURP                                |
| 2. Can treat patients while anticoagulated  | 2. No tissue for path with coagulation necrosis techniques            |
| 3. No TUR syndrome  | 3. Longer catheter times with coagulation necrosis techniques         |
| 4. ↓ irrigation use   | 4. Prolonged irritative symptoms with coagulation necrosis techniques |
| 5. ↓ retrograde ejaculation   | 5. Expensive generators and fibres                                    |
| 6. Short learning curve   |   |
| 7. Perhaps less expensive if shorter hospital stay and fewer complications included |   |

### What are the methods of delivery of laser energy into the prostate?

- End-firing (contact): bare, sculptured, or sapphire tip
  - removes tissue immediately, decreasing post-tx voiding difficulties
- Side-firing: metal or glass reflector, prismatic internal reflector
  - fiber bends laser beam at various angles
  - reflective system w/ gold-plated mirror or solid gold tip to deflect beam
  - coagulation most often used: beam applied until treated area becomes white, then move on
  - difficult to control distribution of energy and predicting eventual result
- Interstitial: bare or diffuser tip +/- temperature transducer
  - integrity of prostatic urethra preserved
  - small fiber introduced into prostate, and Nd:YAG or diode laser used to heat prostate and induce coagulative necrosis
  - necrotic tissue removed by tissue repair → not sloughed and passed like others

### How does laser energy affect the prostate?

- increases local temperature
  - T 45-50°C: desiccation of tissue
  - T 70-90°C: coagulation begins
  - T > 100°C: tissue boils w/ carbonization and vaporization
- during vaporization, water converted to steam → mini-explosions in tissue, increasing mechanical rupture

### How does one perform a HoLEP?

- 26F continuous flow modified resectoscope
- median lobe resected by initial bilateral BN incisions and transverse incision just proximal to veru
- median lobe undermined to BN and detached into bladder
- lateral lobes removed by making incisions at 1 and 5 o'clock, 7 and 11 o'clock, and undermining proximally
- lobes morcellated or removed if small

### What are the complications of VLAP?

- retrograde ejaculation: 27-33%

## Chapter 40 Questions - TURP.doc

- strictures: 0-2%
- BN contracture: 4%
- post-op retention: 30%

### What are the results from using lasers for TURP?

- TULIP
  - not used anymore
  - 68% improvement in sx score, 78% increase in PFR
  - high incidence of complications, reoperation in 15-20%
- VLAP
  - increase in PFR from 7-15cc/sec, decrease in sx score from 20-10 at 3mo, down to 5.7 by 3y
  - PdetQmax decreases from 74 to 54
  - urodynamically proved obstruction: 80% preop, 5% 6mo postop
  - less OR time/hospitalization vs. TURP, but less improvement in PFR and sx score
  - **has been shown to be safe on pts w/ full anticoagulation**
  - no TURP syndrome
- HoLEP
  - improvement in sx score from 21 to 7, increase in PFR from 9 to 21 cc/sec
  - low complication rate

### What are the indications for TURP?

- Absolute
  - stones, hematuria, infection, tics, retention, renal failure
- Relative
  - pt w/ bothersome symptoms of BOO

### Describe the technique of TURP.

- Pre-op
  - Workup
    - urinalysis: r/o UTI as cause of sx
    - DRE
    - Cr
    - UDS: flow, PVR, P-F studies
    - CMG: not recommended routinely
    - cystoscopy: not recommended as means to determine if tx necessary
    - TRUS
    - upper tract imaging: not recommended routinely
  - pre-op antibiotics: IV Ancef +/- gent
  - informed consent and risks: UI, ED, retrograde ejaculation, TUR syndrome, LUTS
- Procedure
  - GA or spinal
  - nonhemolytic solution: 1.5% glycine, cytol
    - not isotonic solutions: 200mOsm/L
  - scrub perineum
  - calibrate urethra: dorsal VIU w/ #12 blade if meatus too snug
  - PU if needed
  - complete endoscopy
  - Nesbit technique
    - 1<sup>st</sup> stage: resect BN from 12 to 9 o'clock until see circular fibers of BN
      - ◆ incise BN at 6 o'clock in small glands if appears to be obstructing
    - 2<sup>nd</sup> stage: resect adenoma in quadrants, superiorly to inferiorly
      - ◆ don't undermine trigone
    - 3<sup>rd</sup> stage: adenoma removed immediately proximal to EUS, preserving veru
- Post-op
  - PO antibiotics until cath removed

### What is the TUR syndrome?

- excessive absorption (>2L) of TUR irrigation fluid which leads to hypervolemia and dilutional hyponatremia
  - 20cc/min fluid absorbed by pt, dependent on height of bags
  - more fluid absorbed when height of fluid > 60-70cm

## Chapter 40 Questions - TURP.doc

- decreased serum osmotic pressure and fluid shifts → pulmonary and cerebral edema
- conversion of glycine to glycolic acid +  $\text{NH}_4^+$  (? $\text{NH}_4^+$  toxicity)

### What are the RF for developing the TUR syndrome?

- prostate >45g
- resection time >90min
- deep resection with open veins
- lots of irrigant used

### What are the manifestations of TUR syndrome?

- Sx/signs: usually occur when  $\text{Na}^+ < 125$ 
  - CVS: angina, syncope, CHF, htn, bradycardia, increased CVP, CVS collapse, pulmonary edema
  - neuro: apprehension, disorientation, confusion, visual changes, headache, stupor, seizures, coma
  - GI: N/V
  - hypothermia (from cold irrigant)
  - tachypnea
- Labs: CBC, lytes, BUN, creat, BS, osmolality, ammonia, glycine, ABG, ECG
  - hyponatremia (if  $\text{Na} < 120$  = severe) and hypochloremia
  - K normal or slightly up: transmembrane electrolyte exchange or hemolysis
  - osmolality usually unchanged → may get osmolality gap due to glycine (not included in calculated osmolality)
  - increased ammonia, lactate → acidosis
  - hemolysis
  - ECG changes: widening of QRS, ST changes, VT or VF

### What is the DDx of the TUR syndrome?

- extravasation
- PE
- hypovolemia
- MI
- sepsis

### What is the treatment of TUR syndrome when it is recognized?

- STOP TURP as soon as possible and control hemorrhage
- mild sx: N/V, agitation, confusion
  - check lytes, monitor, give loop diuretic (Lasix) or osmotic diuretic (Mannitol) if volume overload
  - visual disturbance: ophthalmology consult to r/o other causes (if normal, reassure patient that vision will return)
- severe sx: comatose pt
  - Basic principles of resuscitation
    - Assure oxygenation and airway protection
    - Maintain circulation
    - Decr intracranial pressure (hyperventilate and mannitol)
    - Stop seizures (diazepam or lorazepam IV)
    - Correct electrolyte and acid-base imbalances
    - Treat infections
    - Adjust body temperature
  - Specific treatment
    - hypertonic saline if normal renal function (3% saline)
      - ◆ 200cc 3% NS over 1-2h, measure lytes, then another 100cc prn
    - HD if renal failure
    - sodium bicarbonate if hypertonic saline not available
    - Ca if acute decr calcium
    - furosemide or mannitol to decr fluid overload
  - Calculate Na requirements based on TBW and administer this amount as 3% NS
    - 60% of TBW = fluid (42L): 40% intracellular ( $2/3$ ) = 28L, 20% extracellular ( $1/3$ ) = 14L,
      - ◆ 4% plasma (2.8L), 16% interstitial (11.2L)
    - Actual ECF volume in the post op patient = Normal Na / Post-op Na x TBW x (20%)
    - Amount of irrigant absorbed = Actual ECF volume - TBW (20%)
  - ex: 70 kg male w/ post op Na of 100
    - Actual ECF volume post-op =  $(140/100) \times 70 (0.2) = 1.4 \times 14\text{L} = 19.6\text{L}$
    - Amount of irrigant absorbed =  $19.6\text{L} - 14\text{L} = 5.6\text{L}$

## Chapter 40 Questions - TURP.doc

- Amount of sodium required to bring [Na] back to normal
- $= (\text{preop Na} - \text{postop Na}) \times \text{TBW} (0.2) = (140-100) \times 70 (0.2) = 560 \text{ meq of Na}$
- Amount of Na in 3% hypertonic saline = 513 meq/L
- Therefore, need approximately 1L of hypertonic saline

### How can one prevent TUR syndrome from occurring?

- limit OR time to 1 hour
- hydrostatic pressure of irrigating fluid < 70 cm water
- spinal anesthetic: detects early signs of cerebral symptoms earlier
- decreased BP with spinal anesthetic should be treated with vasopressor rather than fluid boluses
- avoid hypotonic IV solutions
- rapid serum electrolyte determination available
- use continuous flow resectoscope or SP tube

### What are the clinical outcomes after TURP?

- improvement of pt sx in 88%
- decrease in sx score by 85%

### What are the complications of TURP?

- Intra-op
  - Local
    - bleeding
      - ◆ clot retention (3%)
      - ◆ transfusion (1-4%)
    - perforation of prostate capsule (2%), BN, bladder
    - persistent erection
      - ◆ tx: wait, ice NS gauze at base of penis, muscle relaxants, parasympatholytics, aspiration, ICI, stop OR, PU
    - obturator spasm
    - undermining of BN
    - damage to EUS
    - fragmentation of a prostatic lobe (unable to retrieve prostatic chips because of size)
    - burn injury
    - intravesical explosion
    - injury to ureteric orifices
    - extravasation
      - ◆ sx: restlessness, N/V, LBP/abdo pain despite anaesthesia
      - ◆ SP drainage if concern re: infected tissue
    - rectal injury
  - Systemic
    - TURP syndrome
    - infection/sepsis
- Postop
  - Immediate
    - Local
      - ◆ bleeding + clot retention
      - ◆ failure to void (6.5%), +/- replacement of catheter (4%)
      - ◆ UTI: pyelo, cystitis, urethritis, meatitis
      - ◆ catheter malfunction: blockage, failure to deflate
    - Systemic
      - ◆ TUR syndrome
      - ◆ DIC
      - ◆ haem: stroke, DVT/PE
      - ◆ CVS: MI, shock, arrhythmia, CHF
      - ◆ GI: ileus, stress ulcers, acalculous cholecystitis
      - ◆ CNS: stroke, neuropraxia from positioning, residual paresthesia from spinal anesthetic
      - ◆ infection, sepsis
      - ◆ death: 1%
  - Delayed
    - Local
      - ◆ delayed bleed: sloughing of ischemic tissue



## Chapter 40 Questions - TURP.doc

- ◆ BN contracture
- ◆ urethral stricture
- ◆ need for 2<sup>nd</sup> TURP
- ◆ ED: 4-10%
- ◆ UI: up to 4%
- ◆ UTI
- ◆ meatal stenosis
- ◆ retrograde ejaculation: 100%
- ◆ adenoma regrowth and need for 2<sup>nd</sup> TURP (10% risk at 10yrs)

### What is the etiology of hemorrhage post TURP?

- Arterial bleeding
- Venous bleeding
  - Capsular perforation
- Coagulopathy
  - primary (ATIII deficiency, low platelets, uremia, etc.)
  - medication related (coumadin, heparin, ASA)
  - secondary (from TUR syndrome)

### How does one deal with severe bleeding from TURP?

- Intraoperative
  - General measures
    - ABC: airway, breathing, circulation (if hypotensive, bolus with crystalloid/NS or colloids/albumin)
    - X&T, stat CBC/coags
    - 2 large bore IVs
    - correct coagulopathy if present
  - Local measures
    - Arterial – fulgurate
      - ◆ slow inflow to locate arterial bleeders, resect to expose hidden sites, inspect contralateral wall
    - Venous - fulguration
      - ◆ insert catheter, blow up balloon and tamponade
      - ◆ Foley balloon to traction x 10 minutes + irrigate → if venous bleeding, colour should improve
  - Systemic
    - correct any coagulopathy
    - transfuse: pRBC, cryo, platelets, FFP
- Postoperative
  - General measures
    - ABC: airway, breathing, circulation (if hypotensive, bolus with crystalloid/NS or colloids/albumin)
    - X&T, stat CBC/coags
    - 2 large bore IVs
    - correct coagulopathy if present
  - Immediate bleeding in RR = faulty intraoperative hemostasis
    - manual catheter irrigation to declot, then high-flow CBI
    - full balloon (50cc) on traction
    - double balloon catheter
    - iced saline irrigation
    - alum and/or silver nitrate and/or formaldehyde irrigation (usually for TURBT, not TURP)
    - Amicar (intravesically or systemically)
  - Return to OR if fails
    - 2<sup>nd</sup> look to declot, coagulate and rollerball
    - open attempt at hemostasis
      - ◆ suture ligation at BN
        - ♦ Malament stitches: nylon pursestring at BN, bring out through ant abdo wall and remove 1-2d later
        - ♦ O'Connor stitches: plicate posterior prostatic capsule with O-chromic
      - ◆ pack prostatic fossa
      - ◆ place SP tube
      - ◆ ligate internal iliacs
    - radiologic embolization of bleeder
  - Systemic Measures
    - amicar IV 5 g IV loading over 1 hr and then 1 g/hr x 8 hr (up to 30 g/24 hr)

## Chapter 40 Questions - TURP.doc

- correct systemic coagulopathy: cryo, platelets, FFP, vitamin K, protamine
- Delayed bleeding = sloughing of tissue rendered ischemic during initial procedure
- ensure pt stable
- irrigate bladder + CBI
- r/o other causes of hematuria: H&P, labs
- treat other causes if found
- correct systemic coagulopathy
- if bleeding from prostate: traction on Foley, Amicar, cystoscope and fulgurate

### How does TUVF work?

- electrosurgical vaporization and desiccation
  - vaporization at leading edge of electrode, desiccation at trailing edge
- complications and efficacy similar to TURP

### What electrodes can be used for TUVF?

- rollerball
  - should not be used for excessively large prostates
- grooved rollerbar
  - superior to rollerball as grooved design increases the # of leading edges at which electrovaporization will occur
  - increased efficiency

### Describe the technique of TUIP.

- Collins knife: incision at 5 and 7 o'clock, or only on 1 side
- start just distal to UO, end just proximal to veru
- incision depth to pt where external capsule seen

### What are the complications of TUIP?

- retrograde ejaculation: 0-37%

### What are the results after TUIP?

- less effective than TURP for relieving obstruction
- **procedure most useful in pts w/ small prostate and obstructive LUTS → younger man, prostate < 30cc**
- decrease in sx score from 12.5→7, increase in PFR from 10→15cc/sec, PVR decrease from 180→100cc, PdetQmax decrease from 85→45cmH<sub>2</sub>O
- improvement in flow rate better w/ TURP, but more retrograde ejaculation

### What are the indications for TUIP?

- younger sexually active patients
- small gland
- older sick patients

### What are the advantages and disadvantages of the various modalities for endoscopic management of BPH?

- TUIP
  - Advantages
    - short hospitalisation
    - no fluid absorption
    - shorter operative time
    - little bleeding
    - decr incidence of retrograde ejaculation
    - decr incidence of bladder neck contracture
  - Disadvantages
    - not optimal for treatment of large median lobe, AUR, hematuria, prostatitis
    - large prostate may require several passes
    - postoperative urinary retention often seen
    - no tissue for histology
    - success rate not known yet
- High-frequency focused ultrasound (HIFU)
  - Advantages: safe
  - Disadvantages
    - no long-term data

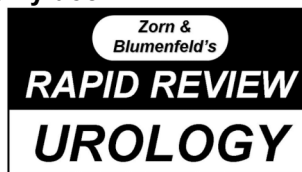
## Chapter 40 Questions - TURP.doc

- can't treat median lobe
- Laser Prostatectomy (TULIP, VLAP, HoLRP, interstitial)
  - Advantages
    - no bleeding
    - no TUR syndrome
    - less irrigation
    - can treat patients while anti-coagulated
    - less retrograde ejaculation
    - shorter hospital stay (and maybe cheaper)
  - Disadvantages
    - less long-term data than TURP
    - no tissue for path (unless HoLRP)
    - longer catheter times with coagulation necrosis techniques (VLAP, TULIP, interstitial)
    - longer irritative voiding symptoms with coagulation necrosis techniques
    - expensive equipment
- Prostatic stents and coils (temporary or permanent)
  - Advantages
    - short operative time
    - no hospitalization
    - no GA needed
  - Disadvantages
    - no tissue
    - no long term follow-up
- TUMT
  - Advantages
    - safe
    - outpatient
    - low morbidity
    - no retrograde ejaculation
  - Disadvantages
    - cost
    - transient urinary retention in up to 40%
    - no tissue
    - not as effective as TURP
- TUNA
  - Advantages
    - no retrograde ejaculation
    - can do under local +/- sedation
  - Disadvantages
    - 20% transient retention rate
    - does not Rx median lobe or BN
    - no RCT data vs. TURP/TUMT
- Circumventing the problem (CIC, SP, Foley)
  - Advantages
    - no anesthetic risk
  - Disadvantages
    - infection
    - erosion
    - stones and encrustation
    - catheter blockage

**What modalities of treatment have minimal retrograde ejaculation but don't treat median lobe?**

- TUIP
- TUMT
- TUNA
- HIFU





## **Chapter 41**

### **• Retropubic and Suprapubic Open Prostatectomy •**

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#### **What are the advantages and disadvantages of open prostatectomy (vs. TURP)?**

- Advantages
  - lower retreatment rate
  - more complete removal of prostatic adenoma under direct vision
  - avoids TURP syndrome
- Disadvantages
  - midline incision
  - longer hospitalization and recovery
  - increased bleeding

#### **What is the difference b/w retropubic and suprapubic prostatectomy?**

- retropubic = enucleation of adenoma through direct incision of anterior prostatic capsule (via RP approach)
- suprapubic = transvesical = enucleation of adenoma through extraperitoneal incision of lower anterior bladder wall

#### **What are the advantages and disadvantages of retropubic vs. suprapubic prostatectomy?**

- Retropubic
  - Advantages
    - excellent anatomic exposure
    - direct visualization of adenoma to ensure complete removal
    - precise transection of urethra distally
    - clear visualization of prostatic fossa after enucleation to control bleeding
    - minimal/no surgical trauma to bladder
  - Disadvantages
    - no direct access to bladder: cannot remove stone or excise diverticula
- Suprapubic
  - Advantages
    - allows direct visualization of the BN and bladder mucosa
    - suited for pts w/ large median lobe, diverticulum, or bladder stones
  - Disadvantages
    - reduced visualization of the apical prostatic adenoma
    - more difficult hemostasis due to inadequate visualization of prostatic fossa

#### **What are the indications and contraindications for open prostatectomy?**

- Indications
  - same as TURP: SHITRR
  - consider open prostatectomy if:
    - estimated obstructive tissue > 75g
    - sizeable bladder diverticula or stones that require removal
    - orthopedic conditions that prevent proper lithotomy for TURP
    - recurrent or complex urethral conditions: strictures, previous hypospadias repair
    - associated inguinal hernia: can be repaired through same incision
- Contraindications
  - small fibrous gland
  - prostate cancer
  - previous TURP
  - pelvic surgery that may obliterate access to prostate gland

#### **Describe the technique of retropubic prostatectomy.**

- Pre-op
  - Evaluation

## Chapter 41 Questions - Open prostatectomy.doc

- Hx, IPSS
- PVR
- cysto: if hematuria, stricture, stone, tics
- PSA, DRE: r/o prostate ca
- upper tract evaluation: if known renal disease, abnormal renal fn, recurrent UTI, hematuria
- stop anticoagulation
- CBC, lytes, Cr, U/A
- CXR, ECG
- Fleet
- Procedure
  - spinal or epidural
  - supine, break table
  - 22F Foley, prep
  - lower midline incision, separate rectus belly
  - enter space of Retzius
  - mobilize peritoneum
  - inspect for hernias
  - gain control of dorsal venous complex and lateral pedicles at BN
    - endopelvic fascia incised laterally
    - puboprostatics partially transected
    - tie off dorsal venous complex w/ 3-0 Monocryl on 5/8 needle
    - tie off lateral pedicles w/ large chromic on CTX needle at prostatovesicular junction: figure of 8 tie
  - 15 blade to make transverse incision in prostate 1.5-2cm distal to BN
  - incision deepened to level of adenoma, extended laterally
  - Metz used to dissect capsule off adenoma
  - index finger used to dissect bluntly
  - Metz used to divide urethra
  - 4-0 chromic used to place figure-of-8 stitch in BN at 5 and 7 o'clock positions
    - must visualize UOs
  - place 22F 3-way catheter into bladder
  - close prostatic capsule w/ 2-0 chromic
  - JP drain, SP
  - close rectus, skin
- Post-op
  - traction on Foley if ++ bleeding
  - CBI
  - cysto + fulgurization if bleeding persists, re-exploration if continues
  - remove Foley POD2
  - SP removed POD5

### Describe the technique of suprapubic prostatectomy.

- 22F Foley, fill bladder w/ 250cc water
- lower midline incision, separate rectus
- enter space of Retzius
- 2 3-0 stitches placed on each side of the midline below peritoneal reflection
- vertical cystotomy w/ electrocautery, continue w/ Metz to within 1cm of BN
  - figure of 8 w/ 3-0 Vicryl at uppermost edge of cystotomy to prevent extension during blunt dissection
- retractor placed
- electrocautery used to create circular incision in bladder mucosa distal to trigone
- plane b/w adenoma and capsule developed at 6 o'clock w/ Metz
- bluntly develop w/ finger posteriorly towards apex
  - pinch off urethra: do not avulse
- lobes removed
- prostatic fossa inspected for residual tissue
- control bleeding w/ cautery or 4-0 chromic
- place 0-chromics in 2 figure-of-eight sutures at 5 and 7 o'clock at prostatovesicular junction to control main arterial supply
  - if bleeding continues, place #2 nylon purse string around BN, brought out to skin and tied firmly: can be cut later
- 20-24 SP Malecot, 22F Foley
- close cystotomy in 2 layers

## **Chapter 41 Questions - Open prostatectomy.doc**

- JP drain
- close rectus, skin

### **What are the complications of open prostatectomy?**

- bleeding: 5-10% risk transfusion
- urinary extravasation: usually resolves
- LUTS: may be present for few mo, tx w'/ anticholinergics
- UI: if SUI, consider injections or AUS
- ED: in 3-5%
- retrograde ejaculation: in 80-90%
- UTI
  - epididymitis, cystitis
- BN contracture: 2-3%, 6-12 weeks postop
  - initial management is dilation or TUIBN
- stricture
- DVT/PE, MI, stroke: <1%
- death: almost 0%

### **What are the results after open prostatectomy?**

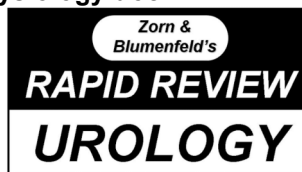
- PFR, sx score: superior to all other tx, including TURP

### **What hemostatic maneuvers can be used during open prostatectomy?**

- control of dorsal venous complex – as per RRP
- parallel transverse capsular sutures (Millen technique)
- ligation of the prostatovesical vessels
- oversewing of capsular bleeders
- approximation of BN mucosa to the prostatic floor
- temporary nylon purse-string suture of the bladder neck (removed POD#1-2)







## Chapter 42

### • Male Reproductive Physiology •

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#### **Describe the hypothalamic-pituitary-testis axis.**

- hypothalamic neurons in preoptic area w/ axons projecting to median eminence secrete GnRH into portal system of blood vessels leading to pituitary
- anterior pituitary contains gonadotropes: stimulated by GnRH to secrete LH and FSH
  - LH stimulates T production by Leydig cells in interstitium
  - FSH stimulates Sertoli cells for spermatogenesis
    - FSH not essential for spermatogenesis → stem cell factor (secreted by Sertoli cells) binds to cell surface receptors in spermatogonia / spermatocytes / round spermatids
    - optimal quantitative and qualitative spermatogenesis requires FSH
- T and estradiol suppress secretory activity by GnRH neurons and gonadotropes
  - **T acts primarily to feedback at level of hypothalamus**
  - -ve effects on LH primarily by androgen itself
  - **estradiol provide feedback to pituitary** to modulate LH/FSH secretion response to each GnRH surge
  - -ve effects on FSH primarily by estradiol
- inhibin secreted by Sertoli cells: suppresses FSH secretion
- activins secreted by Sertoli cells stimulate FSH secretion, inhibited by follistatins

#### **Describe the temporal rhythms of GnRH and LH secretion.**

- 3 types of GnRH rhythms:
  - seasonal: peaking in spring, changing over months
  - circadian: highest T levels in early morning
  - pulsatile: peaks q90-120min
- LH secreted at pulses q2hrs

#### **What is Kallman's syndrome?**

- congenital hypogonadotropic hypogonadism
  - GnRH precursor neurons fail to migrate normally → no capacity for hypothalamic secretion of GnRH
  - olfactory deficiency and other midline defects + hypogonadism

#### **Describe the anatomy of the pituitary.**

- posterior lobe (neurohypophysis)
  - formed during development as outpouching of hypothalamus
  - 2 hormones: oxytocin and vasopressin → driven by neural stimuli
- anterior lobe (adenohypophysis)
  - glandular structure regulated by blood borne factors
  - gonadotropes: secrete LH and FSH
  - corticotropes: secrete ACTH
  - lactotropes: secrete PRL
  - somatotropes: secrete GH
  - thyrotropes: secrete TSH

#### **Describe the development of the hypothalamic/pituitary axis from birth to puberty.**

- placenta secretes hCG → stimulates development of Leydig cells
- 7<sup>th</sup> week: Leydig cells differentiate from mesenchymal precursor cells in CT stroma of testis b/w seminiferous tubules
- fetal Leydig cells regress after birth
- 2-3 months after birth: LH surge from pituitary → stimulates 2<sup>nd</sup> wave of Leydig cells, increasing T in male infants
  - T hormonally imprints hypothalamus, liver, prostate, penis
- Leydig cells regress until puberty
  - T produced is metabolized to androstenediol (weak affinity to AR, -ve feedback delayed)
- hypothalamus can generate GnRH pulses starting at puberty

## Chapter 42 Questions - Reproductive Physiology.doc

### How does the hypothalamic/pituitary axis change w/ age?

- men > 50: serum T decreases
- LH pulses blunt
- Leydig cell steroidogenic capacity decreases

### Describe the anatomy of the testis.

- volume 15-25cc, length 4.5-5cm
- 3 layers in capsule: visceral tunica vaginalis, tunica albuginea, innermost tunica vasculosa
  - smooth muscle cells in tunica albuginea: may have contractile ability, regulate blood flow into testis
- testis divided into compartments within capsule separated by septa
  - each septa separates seminiferous tubules, contains 1 or more centrifugal artery
- interstitial tissue in each septum
  - contains individual seminiferous tubules(?), Leydig cells, mast cells, macrophages, nerves, lymph and blood vessels
- seminiferous tubules are long V-shaped tubules: both ends terminate in rete testis
  - 600-1200 tubules in testis
- rete testis coalesce to form 6-12 ductuli efferentes (efferent ducts)

### Describe the vascular supply to the testis.

- Arterial
  - 3 sources:
    - gonadal/testicular/spermatic artery
    - vesiculodeferential artery (from internal iliac→superior vesical artery)
    - cremasteric artery (from inferior epigastric)
  - number of arteries
    - single artery: 56%
    - 2 branches: 31%
    - 3 or more branches: 13%
  - testicular artery becomes highly coiled and branches before entering testis
    - branches to internal artery, inferior testicular artery, and artery to epididymal head
  - testicular arteries penetrate tunica albuginea travel inferiorly along posterior surface of testicular parenchyma
    - branches pass anteriorly in transverse fashion over parenchyma
    - medial and lateral midsection of testis have fewer vessels
  - artery divides into centrifugal arteries that penetrate parenchyma
    - branches into arterioles that supply individual intertubular and peritubular capillaries
    - intertubular capillaries: inside columns of interstitial tissue
    - peritubular capillaries: run near seminiferous tubules
- Venous
  - do not run w/ corresponding intratesticular arteries
  - small veins in parenchyma empty into veins on surface of testis or into group of veins in mediastinum
  - join w/ deferential veins to form pampiniform plexus
    - pampiniform plexus: allows for countercurrent heat exchange
- Lymphatic
  - originate in intertubular spaces: do not penetrate the seminiferous tubules
  - seminiferous tubules do not drain into lymphatics
    - ECF bathing Sertoli and germinal cells flows from seminiferous tubules into rete to form rete testis fluid
      - ◆ rete testis fluid is a dilute suspension of sperm in a fluid isoosmotic w/ plasma
    - transported into caput epididymis

### Describe the innervation to the testis.

- no somatic innervation
- autonomic sympathetic innervation
  - from thoracic/lumbar splanchnic nerves to renal and aortic plexus, travels w/ gonadal vessels
  - from superior hypogastric plexus to pelvic plexus, travels w/ vas

### What is the function of the Leydig cell?

- responsible for the bulk of steroid production

### What are the steps of testosterone production in the Leydig cell?

- LH binds to its R

## Chapter 42 Questions - Reproductive Physiology.doc

- LH R has 7 membrane-spanning domains, coupled to G proteins (Gi, Gs)
- adenyl cyclase stimulated to produce cAMP, which stimulates protein kinase A
- LH also stimulates:
  - Ca influx → calmodulin activation of Ca/calmodulin kinase
  - arachidonic acid mobilization from PLA<sub>2</sub>
  - efflux of Cl
- T produced from cholesterol → 3 main sources:
  - cholesterol derived from blood plasma: internalization of cholesterol/lipoprotein receptor complexes
  - synthesized de novo from acetate
  - stored cholesterol esters in lipid droplets
- cholesterol transported into mitochondria → inner membrane
  - moved by 2 transport proteins: steroid acute regulatory protein (StAR) and peripheral benzodiazepine receptor (PBR)
  - StAR signal sequence allows StAR protein to pass through mitochondrial membrane
  - PBR forms channel for cholesterol in mitochondrial membrane
- cholesterol side-chain cleavage enzyme (P450<sub>sc</sub>) converts it to pregnenolone and C6 fragment isocaproaldehyde
  - pregnenolone transported out of mitochondrial membrane into sER
  - converted into T in ER
- T diffuses across cell membrane
  - trapped in ECF and blood plasma by steroid-binding proteins albumin and SHBG

### How does T concentration in the serum change during the life cycle?

- 3 peaks of T:
  - in human fetus at 12-18 weeks → causes differentiation and development of fetal reproductive tract
  - neonatal: 2 months → causes imprinting of androgen-dependent target tissues
  - maximum concentration during 2<sup>nd</sup> or 3<sup>rd</sup> decade → causes masculinization of male at puberty
    - reaches plateau, and decline → maintains growth and function of androgen-dependent organs

### What are the components and structure of the seminiferous tubule?

- peritubular structures
  - outer layer of fibrocytes → separate interstitium from seminiferous tubules
  - middle layer of myoid cells interspersed w/ connective tissue lamellae
    - primarily contractile function
    - secrete **fibronectin** and **type I collagen**
    - also secretes paracrine factor **P-Mod-S** (peritubular modifies Sertoli): stimulates Sertoli cell function and differentiation
  - inner layer of collagen
- Sertoli cell
  - irregularly shaped nucleus, prominent nucleolus
  - rests on BM of seminiferous tubule, extends cytoplasmic filaments towards lumen of tubule
  - undifferentiated spermatogonia sit near BM, more advanced spermatocytes near lumen
- blood-testis barrier
  - specialized junctional complexes b/w adjacent Sertoli cells
  - presence of germ cells not needed for development of BTB
  - 3 different levels:
    - tight junctions b/w Sertoli cells: segregate spermatogonia from other germ cells
      - ◆ during extended meiotic prophase, spermatocytes move out from basal compartment to adluminal compartment
    - endothelial cells in capillaries
    - peritubular myoid cells

### What are the secretory products of the Sertoli cell?

- **ABP** (androgen binding protein): function unknown (?intracellular carrier of androgen in Sertoli cell)
- **ECM components**: laminin, type IV collagen, type I collagen
- **proteins**: ceruloplasmin, transferrin, glycoprotein 2, plasminogen activator, inhibin, H-Y antigen, clusterin, etc
- **steroids**: DHT, T, androstenediol, 17β-estradiol, other C21 steroids

### How does a testicular insult cause antisperm antibodies?

- antigens on germ cells present only after initiation of puberty
- biopsy, torsion, trauma causes **ASA production only if insult occurs after puberty**

## Chapter 42 Questions - Reproductive Physiology.doc

### What are the different compartments created by the Sertoli cell?

- basal compartment: next to BM
  - spermatogonia and early spermatocytes share positions on basal lamina, covered by processes of Sertoli cell that form BTB
- intermediate compartment
  - Sertoli cells form junctional complexes above and below spermatocytes being transported to adluminal compartment
- adluminal compartment
  - elongating spermatids sit in trunk of Sertoli, moves toward lumen

### What are the steps of spermatogenesis?

- entire process takes 64 days
  - helical arrangement of stages in the seminiferous tubule
  - 6 stages of spermatogenic cycle can be seen
- proliferative (mitotic) phase: differentiation of Ap to B spermatogonia
  - stem cell renewal: spermatogonia divide to replace their number via mitosis
    - little change until age 7, mitosis detectable during age 7-9, and little change until puberty
    - of each cell produced by mitotic division, one stays as spermatogonia, other becomes cell line that gives rise to 16 spermatids
  - production of daughter cells to become spermatocytes
    - pale type A spermatogonia (Ap) divide at 16d intervals to form B spermatogonia
      - ◆ 4 cohorts of differentiating sperm cells seen in seminiferous epithelium
    - B spermatogonia committed to become spermatocytes
    - type B spermatogonia interconnected by cytoplasmic bridges
      - ◆ divide mitotically to form primary spermatocytes
      - ◆ each spermatogonium undergoes 2 mitotic divisions to form 4 primary spermatocytes
- meiotic phase: primary spermatocytes undergo reduction division → results in haploid spermatids
  - meiotic prophase: primary spermatocyte → leptotene spermatocyte (L) → zygotene spermatocyte (Z) → pachytene spermatocyte (P) → secondary spermatocyte
  - primary spermatocytes undergo 1<sup>st</sup> meiotic division to form 2 secondary spermatocytes
  - each secondary spermatocytes undergo 2<sup>nd</sup> meiotic division to form round Sa spermatids (4 from each primary spermatocyte)
- spermiogenesis: spermatids form mature spermatozoa
  - round Sa spermatids → Sb<sub>1</sub> → Sb<sub>2</sub> → Sc → Sd<sub>1</sub> → Sd<sub>2</sub>

### What cytoplasmic changes occur during spermiogenesis?

- loss of cytoplasm
- formation of the acrosome
- formation of the flagellum
- migration of the cytoplasmic organelles

### How do Y-chromosome microdeletions affect spermatogenesis?

- deletion of region of Y chromosome called interval 6 present in 5-10% of azoospermic men
  - site of critical factor called AZF (Azoospermic Factor) important for spermatogenesis
- several regions on Y chromosome seen:
  - AZFc: gene called DAZ (deleted in azoospermia) localized to AZFc
  - AZFa: complete deletion of AZFa uniformly causes azoospermia w/ SCO pattern
  - AZFb: critical to completion of spermatogenesis

### Describe the anatomy of the epididymis.

- 3-4m in length
- coiled, encapsulated within sheath of connective tissue of the tunica vaginalis
- divided into 3 regions
  - caput (head)
    - consists of 8-12 efferent ducts and proximal segment of the ductus epididymis
    - lumen of efferent ducts are large and irregular near testis, becoming narrow and oval near junction w/ ductus epididymis
  - corpus (body)
    - diameter increases slightly, remains constant throughout body of epididymis
  - cauda (tail)

## Chapter 42 Questions - Reproductive Physiology.doc

- diameter increases greatly, and lumen becomes irregular
- contractile cells site external to BM of efferent ducts
  - form loose layer 2-4 cells deep, containing myofilaments
  - replaced in cauda by thick smooth muscle cells that form 3 layers: outer and inner longitudinal, middle circular

### What is the innervation of the epididymis?

- derive from intermediate and inferior spermatic nerves
  - arise from superior portion of hypogastric plexus and pelvic plexus
- efferent ducts and proximal epididymis innervated by sympathetics
- responsible for rhythmic peristaltic movements: move sperm through epididymis

### Describe the vascular supply to the epididymis.

- Arterial
  - single branch from gonadal artery supplies head and body of epididymis
    - divides into superior and inferior epididymal branches
  - branches of vesiculodeferential artery
- Venous
  - drainage from head and body of epididymis join to form vena marginalis epididymis of Haberer
  - capital veins communicate w/ pampiniform plexus
- Lymphatic
  - 2 routes:
    - head and body: removed through same vessels that drain testis
      - ◆ follow gonadal veins through inguinal canal, drain to preaortic nodes
    - tail: join those draining vas, go to external iliac nodes

### Describe the histologic structure of the epididymis.

- junction of rete and efferent ducts: transition from low to high cuboidal
- efferent ducts: ciliated cells and 2 types of nonciliated cells
  - ciliated cells interspersed
  - secretory nonciliated cells predominate in proximal efferent ducts
  - resorptive nonciliated cells w/ microvilli predominate in distal efferent ducts
- ductus epididymis: 2 major cell types
  - principal cells: absorptive and secretive processes
  - basal cells: rest on basal lamina, derived from macrophages

### What are the functions of the epididymis?

- Sperm transport
  - takes 2-12 days to transport through epididymis
    - transit times: 0.7d (head), 0.7d (body), 1.8d (tail)
  - "recent emissions" decrease transit time through epididymal tail only
  - human sperm immotile in epididymal lumen
    - carried initially into efferent ducts by rete testis fluid
    - motile cilia and contraction of myoid cells in efferent ducts move sperm into epididymis
- Sperm storage (and removal)
  - sperm retained in head of epididymis for varying lengths of time, depending on sexual activity
  - **fate of unejaculated spermatozoa unknown:** ?phagocytosis of sperm by macrophages in lumen
- Maturation of sperm
  - Motility maturation
    - as sperm progress distally, increase in # of sperm w/ mature motility pattern due to interaction w/ epididymis
      - ◆ may be intrinsic process as well
    - > 50% of sperm in cauda epididymis have mature motility pattern
  - Fertility maturation
    - testicular sperm incapable of fertilizing eggs
    - ability to fertilize eggs gradually acquired as sperm migrate into distal epididymis
    - only sperm from distal epididymis able to bind and penetrate eggs
    - improved fertilization if sperm from distal epididymis used for V-E (vs. more proximal epididymis)

### What biochemical changes occur in sperm during epididymal maturation?

- sperm surface membranes assume increasingly -ve net charge during epididymal transit
- formation of intracellular disulfide bonds: give structural rigidity to head and tail

## Chapter 42 Questions - Reproductive Physiology.doc

- increased capacity for glycolysis
- change in intracellular pH and Ca content
- modification of adenylate cyclase activity
- alterations in cellular phospholipid content

### What are the physiologic requirements for epididymal function?

- requires high amounts of androgen for maintenance of structure and function
  - mediated through DHT
  - castration causes loss of androgen-dependent epididymal proteins, loss of epididymal weight, change in histology, and change in secretion of epididymal fluid
- ability of epididymis to store sperm influenced by sympathetic nervous system
  - denervation causes abnormal accumulation in cauda epididymis and decrease in swimming speed

### Describe the structure of a spermatozoon.

- Head
  - 60um in length (including tail), 4.5um long, 3um wide
  - head consists of nucleus (contains chromatin) and acrosome (contains enzymes for penetration)
- Connecting piece
- Middle piece
  - consists of helically organized mitochondria surrounding a set of outer dense fibers and 9+2 microtubular structure of sperm axoneme
  - outer dense fibers rich in disulfide bonds (gives rigidity)
- Principal piece: outer dense fibers and axoneme continue into principal piece
  - surrounded by fibrous sheath
- End piece: outer dense fibers end before end piece

### Describe the structure of the vas.

- 30-35cm long
- 5 portions
  - sheathless epididymal portion: within tunica vaginalis
  - scrotal portion
  - inguinal division
  - retroperitoneal or pelvic portion
  - ampulla
- outer adventitial connective tissue
- muscular coat: inner and outer longitudinal layer, middle circular layer
  - gradually decreases along length of ductus deferens
- mucosal inner layer
- lumen: 0.05cm in diameter
  - pseudostratified epithelium, decreasing in height along length of ductus
    - composed of basal cells and 3 types of tall thin columnar cells (principal cells, pencil cells, mitochondrion-rich cells)
    - principal cells more frequent proximally, others more frequent distally
  - longitudinal folds simple proximally, more complex distally

### What is the vascular supply to the vas?

- vesiculodeferential artery from superior vesical artery

### What is the innervation to the vas?

- rich supply of sympathetic adrenergic nerves
  - from hypogastric plexus
- ?parasympathetic supply: minor importance

### What is the function of the vas?

- sperm transport
  - immediately before emission, rapid and effective transport of sperm from distal epididymis and proximal vas
    - due to sympathetic stimulation
  - after sexual stimulation and ejaculation, contents of vas propelled back into cauda epididymis
    - distal vas contracts w/ greater amplitude, freq, and duration than proximal vas
    - reversed w/ sexual rest → eliminates excess sperm

## **Chapter 42 Questions - Reproductive Physiology.doc**

- sperm storage
- absorption of phagocytosed spermatozoa
- secretion of glycoproteins

### **What are the steps in fertilization?**

- Deposition of sperm in vagina
- Penetration of cervical mucous plug
- Sperm migration through uterus: takes 5 to 68 minutes
- Capacitation and hyperactivation
- Sperm penetration of cumulus oophorus
- Sperm binding to zona pellucida
  - carbohydrate binding proteins on sperm membrane interact w/ species-specific ZP3 protein in egg zona pellucida
- Acrosome reaction
- Sperm penetration of zona pellucida
- Sperm fusion w oocyte plasma cell membrane
- Cortical granule exocytosis
- Nuclear decondensation
- Nuclear fusion
- Embryo cleavage
- Uterine implantation







**Chapter 43**  
**• Male Infertility •**

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**What is the chance of conception for a normal or infertile couple?**

- Normal
  - 20-25% per month
  - 75% by 6mo
  - 90% by 1 year
- Infertile
  - 25-35% of infertile couples will conceive w/o treatment eventually
  - 23% within 1<sup>st</sup> 2 years, another 10% within another 2 years
  - baseline pregnancy rate of 1-3% per month

**What proportion of cases of infertility are caused by male or female factors?**

- 20% male factor
- 40-50% female factor
  - ovulatory dysfunction: 30%
  - fallopian tube abnormality: 25%
  - endometriosis: 5%
  - cervical mucus abnormality: 4%
  - hyperprolactinemia: 4%
- 30-40% both female and male factors

**What does one attempt to identify in the evaluation of the infertile male?**

- reversible conditions
- irreversible causes that may be managed by ARTs w/ sperm
- irreversible conditions that may not be managed by ARTs, in which couple should be advised to pursue donor sperm or adoption
- significant medical pathology
- genetic or chromosomal abnormalities that may affect pt or offspring

**What is involved in the evaluation of the infertile male?**

- History
  - Sexual hx
    - duration of infertility +/- previous treatments
    - prior pregnancies (with present and previous partners)
    - birth control used
    - frequency of sex, timing of intercourse
    - lubricants used
    - erectile/ejaculatory function
      - ◆ absent/low volume ejaculate: ?retrograde ejaculation, hypogonadism, ED obstruction, CBAVD
  - PMHx
    - Developmental
      - ◆ cryptorchidism: unilateral cryptorchidism slightly decreases fertility, bilateral greatly decreases fertility
      - ◆ age at puberty, gynecomastia, congenital abnormalities of GU tract or CNS
    - Surgical
      - ◆ orchidopexy
      - ◆ pelvic/scrotal/inguinal/retroperitoneal surgery: may affect erectile and ejaculatory function
      - ◆ BN surgery: may cause retrograde ejaculation
      - ◆ herniorrhaphy: injury of vas
      - ◆ hydrocele: injury to vas/epididymis
      - ◆ testicular trauma/torsion: testicular atrophy or creation of ASA
      - ◆ SCI

## Chapter 43 Questions - Infertility.doc

- Medical
  - ◆ UTI, STD, epididymitis
  - ◆ mumps: doesn't affect testis if prepubertal
  - ◆ DM, MS: ejaculatory dysfunction, ED
  - ◆ testis cancer, lymphoma: oligospermia in 60% at time of diagnosis
  - ◆ chemo/rads: spermatogenesis may take up to 5 years to return, due to direct toxicity to dividing germ cells
  - ◆ recent febrile illness: spermatogenesis impaired for 1-3 months
  - ◆ headaches, galactorrhea, impaired visual fields: CNS tumour in pituitary
- Meds
  - ◆ nitrofurantoin, cimetidine, CCB, sulfa, cocaine, smoking, marijuana, caffeine → all impair spermatogenesis
  - ◆ T, anabolic steroid use: hypogonadotropic hypogonadism
- Occupation/habits
  - ◆ exposure to pesticides (gonadotoxic), heat, hot tubs, radiation, cigarettes, EtOH
- Previous infertility evaluation and treatment
- FHx
  - hypogonadism, cryptorchidism, congenital midline defects, CF, intersex states
- Female reproductive hx
  - PMHx including pregnancies and offspring w/ other partners
  - menstrual hx
    - ◆ ovulation evaluation
      - ♦ irregular menses: ovulatory dysfunction → do basal body temperature and midluteal phase progesterone
        - normally have increased temp of 0.4°F for 12-15d after ovulation
      - ♦ serum progesterone
      - ♦ endometrial biopsy
      - ♦ ovarian US
    - ◆ tube evaluation: HSG x 2, laparoscopy
  - infertility evaluation to date
- Physical
  - pts habitus, pattern of virilization, stigmata of liver disease
  - secondary sex characteristics: eunuchoid (Klinefelter's), lack of baldness (androgen deficiency)
  - gynecomastia: estrogen/T imbalance, increase in PRL
  - situs inversus: ?Kartagener's
  - visual fields, thyroid
  - genital examination
    - hypospadias, chordee
    - scrotal contents: testicular masses, testis size, epididymis, presence of vas
    - varicocele
    - mucus quality: spinnbarkeit, ferning
  - DRE: prostatitis
- Labs
  - Semen analysis
  - Hormonal evaluation
    - LH, FSH, testosterone, estrogen, PRL, TSH
      - ◆ hormonal evaluation if indication in hx/px, or if sperm count  $< 10 \times 10^6/cc$
      - ◆ endocrine abnormalities rarely present if sperm concentration  $> 10$  million
      - ◆ isolated T low/borderline: morning and free T
      - ◆ impaired visual fields: PRL → CNS tumour: PRL usually  $> 50$
      - ◆ estrogen excess: gynecomastia, ED, atrophic testis → may be due to morbid obesity
    - GnRH stim test
  - Antisperm Ab
  - Leukocyte staining: % of round cells → 1/3 of pts w/ increased round cells have true pyospermia, rest are immature germ cells
    - $> 1 \times 10^6$  WBC/cc is abnormal: ?infection → do WBC staining to r/o pyospermia
  - Semen cultures: test for *Mycoplasma* or *Chlamydia*
  - Ultrastructural evaluation: EM for detection of abnormalities in mitochondria, outer dense fibers, or microtubules
    - ◆ use in pts w/ very low motility but high viability
- Imaging
  - TRUS +/- seminal vesical aspiration
    - $> 10^6$  sperm seen on seminal vesical aspiration in azoospermic pt = ED obstruction

### Chapter 43 Questions - Infertility.doc

- vasography: used to determine site of obstruction in azoospermic men w/ active spermatogenesis seen on biopsy
  - done only at time of reconstruction
  - not indicated in oligospermic pt w/o evidence of vasal obstruction by hx/px and symmetrical testes
- venography
- scrotal US
- abdo US
- Sperm function testing
  - PCT
  - acrosome reaction
  - SPA (sperm penetration assay)
  - others: hemizona assay, sperm viability assays, ROS testing
- Genetic testing
  - karyotype, Y chromosome microdeletions → indicated in men w/ count  $< 5 \times 10^6$  sperm/cc
- Testicular biopsy

### What medications can affect spermatogenesis?

- Suppression of HPG axis: steroids, cimetidine, DES, cyclosporine, phenothiazine
- Direct gonadotoxicity: ketoconazole, sulfasalazine, valproate, spironolactone, chemotherapy, allopurinol
- Impaired fertilization: CCB, colchicine, NFT, minocycline

### What is involved in the evaluation of the female partner for infertility?

- evaluation of ovulation
  - day 3 FSH
  - progesterone
  - transvaginal US
  - basal body temperature charting
- evaluation of fallopian tubes
  - HSG
  - laparoscopy

### What is the optimal frequency of intercourse for pregnancy?

- q2d
  - too frequent: decreased # of sperm deposited
  - too infrequent: ovulatory period missed (the 5 days leading up to ovulation)

### What lubricants do and do not adversely affect sperm motility?

- bad: Astroglide, Lubafax, KY Jelly, Keri Lotion, Surgilube, saliva
  - use lube only if necessary, use minimal amount
- OK: peanut oil, safflower oil, vegetable oil, raw egg white

### What syndromes that cause infertility are associated w/ URTIs?

- Kartagener's syndrome (immotile cilia syndrome)
  - immotile sperm, immotile cilia, hx of frequent URTIs, and situs inversus
- Young's syndrome
  - recurrent URTI, epididymal obstruction due to inspissation of secretions → azoospermia
- Kallman's syndrome
  - congenital hypogonadotropic hypogonadism associated w/ anosmia, galactorrhea, h/a, visual defects
- Cystic fibrosis
  - almost all pts w/ CF have CBAVD

### How can one classify varicoceles?

- Grade I: small varicocele only palpable during Valsalva
- Grade II: varicocele palpable only if pt standing, not while supine
- Grade III: large varicocele visible, palpable if supine

### What is the definition of a subclinical varicocele?

- presence of multiple veins w/ at least 1  $> 3$ mm diameter on scrotal US
- diameter of  $> 3.5$ mm predictive of clinical varicocele
- **no evidence that treatment of subclinical varicocele will improve pregnancy rate → do not treat**

## Chapter 43 Questions - Infertility.doc

### What is the proper technique for collection of a semen sample?

- maintain consistency in duration of abstinence before collection of specimen
- clean, wide mouthed container
- obtain specimen through masturbation
  - if pt objects, use special condoms designed for sperm collection
  - normal latex condoms: interfere w/ viability of sperm and may have spermicides
  - coitus interruptus: initial ejaculate is lost, bacteria and vaginal secretions may contaminate specimen
- examine within 1-2hrs of collection
- need 2-3 specimens over period of few weeks

### What are the factors examined in a semen analysis?

- Physical characteristics
  - noncoagulable, acidic, low volume semen: CBAVD
  - failure of liquefaction: remains a coagulum, does not change consistency after ejaculation
  - hyperviscous after liquefaction: becomes less of a coagulum, but consistency thicker than normal, forms thick strands
    - cause is controversial
    - perform PCT: if results are normal, disregard consistency
      - ◆ if abnormal: cross-mucus hostility test or in vitro cervical mucus-sperm interaction test
  - volume: low or high
- pH
  - normal semen 7.2: balance b/w acidic prostatic secretions and alkaline SV secretions
  - normal pH, low volume: normal vs. incomplete collection or retrograde ejaculation
  - acid pH, low volume: ED pathology, absent SVs
- Sperm count
  - median count of  $70 \times 10^6/\text{cc}$ 
    - decreasing fertility w/ decreasing counts
      - ◆  $12.5\text{--}25 \times 10^6$  sperm/cc: 44% pregnancy rate
      - ◆  $<12.5 \times 10^6$  sperm/cc: 25% pregnancy rate
  - counting chambers used in which sperm are counted in a grid pattern
  - if zero sperm, centrifuge and examine pellet
- Motility/Agglutination
  - motility = % of sperm that demonstrate flagellar motion
    - 5 pt scale: 0 (no motility), 1 (sluggish/nonprogressive), 2 (slow, meandering forward), 3 (reasonably straight line w/ moderate speed), 4 (straight line w/ high speed)
      - ◆ most common category reported
    - 4 pt scale: A (rapid progressive movement), B (slow/sluggish progressive movement), C (non-progressive motility), D (none)
      - ◆ % sperm falling into each category reported
  - agglutination of sperm: suggests presence of ASA
  - round cells
    - WBC and immature germ cells indistinguishable → estimate # / HPF
  - complete nonmotile sperm: ultrastructural defects w/ live sperm (flagellar defect) vs. dead sperm (necropermia)
- Morphology
  - most labs use rigid criteria for definition of normal sperm
  - borderline forms = abnormal
  - IVF fertility rates with normal count and motility:
    - 91% if morphology  $> 14\%$
    - 37% if morphology  $< 14\%$ 
      - ◆ 7.6% if morphology  $< 4\%$
      - ◆ 64% if morphology 4-14%
- Viability
- Fructose: SVs produce fructose in androgen-dependent process
  - obstructed ED or CBAVD: acidic, noncoagulable, fructose-negative semen, w/ low volume

### What are the WHO reference values for a semen analysis?

- Volume: 2cc or more
- pH: 7.2 or more
- Sperm concentration:  $> 20 \times 10^6$  sperm/cc
- Total sperm #:  $> 40 \times 10^6$  sperm/ejaculate

### **Chapter 43 Questions - Infertility.doc**

- Motility: > 50% w/ grade A+B motility or >25% w/ grade A motility
- Morphology: >15% by strict criteria (?30%)
- Viability: >75% sperm viable
- WBC: <1million/cc

### **What are the causes of small volume ejaculates?**

- obstruction of ejaculatory duct
- androgen deficiency
- retrograde ejaculation
- sympathetic denervation
- CBAVD, UAVD
- medications
- BN surgery

### **What is the workup and management for hematospermia?**

- History: Urinary symptoms, duration, precipitating factors (biopsy, TRUS, etc.), bleeding diathesis, initial (prostate) vs. terminal (SV)
- Physical: bladder, CVAT, DRE, External genitalia
- Work-up: Urine R&M, C&S, cytology, PSA if indicated by age
- If all normal, no further w/u or treatment, and reassure

### **What are the strict criteria for normal sperm morphology?**

- Head
  - 5-6µm length
  - 2.5-3.5µm width
- Acrosome
  - 40-70% of head
- Midpiece
  - <1µm width
  - length 1.5x head length
- Tail
  - 45µm long
  - uniform, uncoiled, unkinked
  - thinner than midpiece
- Cytoplasmic droplets
  - less than ½ of head area
  - in midpiece only

### **What is measured on CASA (computer aided SA)?**

- curvilinear velocity
  - average distance / unit time b/w successive positions of an individual sperm
- straight-line velocity
  - speed of a sperm in a forward direction
- linearity = straight-line velocity / curvilinear velocity
- lateral head displacement
- flagellar beat frequency
- circular movement analysis

### **What is the most common hormonal abnormality seen on routine testing of infertile men?**

- elevated serum FSH
  - indicative of problem w/ spermatogenesis
  - normal FSH does not guarantee normal spermatogenesis
  - < 3% of infertile men have primary hormonal etiology

### **What clinical scenario is associated w/ the following lab values:**

- FSH normal, LH normal, T normal: normal men or obstruction
- FSH increased, LH normal, T normal: isolated spermatogenic failure
- FSH/LH increased, T normal or low: complete testicular failure → 14-15%, usually karyotype problem
- FSH/LH/T all decreased: hypogonadotropic hypogonadism

## Chapter 43 Questions - Infertility.doc

### What are the causes of PRL excess?

- pituitary tumour
- stress
- medications
- medical illness
  - renal failure
- idiopathic
- elevated TRH
- chest wall irritation
- thyroid dysfunction

### What are the diagnostic algorithms based on the following parameters:

- Absent/low volume ejaculate +/- azoospermia (medications, retroperitoneal/BN surgery, ED obstruction, DM, MS, SCI, psychologic, idiopathic, incomplete collection)
- pts w/ normal TRUS + low-volume ejaculate and azoospermia treated like any other pt w/ azoospermia
- r/o incomplete collection or short abstinence period
- postejaculatory urinalysis and repeat SA
  - +ve (more sperm in centrifuged urine than in SA) = retrograde ejaculation → start  $\alpha$ -agonist, bladder wash + IUI
  - -ve (suggests lack of SV contribution): perform TRUS
    - ◆ normal = failure of emission → start  $\alpha$ -agonists, EEJ
    - ◆ abnormal: perform SV aspiration
      - ♦ +ve = ED obstruction → TURED
      - ♦ -ve = ED and epididymal obstruction → TURED and V-E
- Azoospermia
  - vasa absent = CBAVD → CFTR testing, sweat chloride to r/o CF → MESA/IVF, AID, adoption
  - vasa present: testis size
    - normal or unilateral atrophy: get FSH
      - ◆ FSH normal: testicular biopsy
        - ♦ normal = obstructed → V-V or V-E
        - ♦ abnormal = primary testicular failure → TESE/IVF, AID, adoption
      - ◆ FSH high (>2X normal) = primary testicular failure → TESE/IVF, AID, adoption
        - ♦ biopsy only if mean to get sperm for TESE/IVF
    - bilateral atrophy: get FSH
      - ◆ FSH low = hypogonadotropic hypogonadism → get LH/FSH, PRL, head CT/MR
      - ◆ FSH high = primary testicular failure → TESE/IVF, AID, adoption
    - pts w/ primary testicular failure: genetic testing → r/o Klinefelter's, Y chromosome microdeletions
      - ◆ usually irreversible
    - pts w/ secondary testicular failure: treat w/ hormones
- Oligospermia
  - count on SA < 5-10x10<sup>6</sup> sperm/cc: get FSH/LH/T
    - complete hormone evaluation if abnormal
    - isolated FSH elevation = abnormal spermatogenesis, further w/u not needed
  - r/o varicocele
- Asthenospermia
  - ASA
    - +ve for ASA → immunosuppression or ART
    - -ve for ASA: motility testing
      - ◆ >5%: semen cultures + U/A → r/o varicocele, heat, systemic illness, pyospermia
      - ◆ <5%: viability assay
        - ♦ high: electron microscopy to r/o ultrastructural defect → IVF/ICSI
        - ♦ low: TRUS
          - normal: get semen cultures → r/o varicocele, heat, systemic illness, pyospermia
          - abnormal: SV aspiration
            - +ve = ED obstruction → TURED
- Teratospermia
  - often associated w/ oligospermia or asthenospermia
  - r/o absence of the acrosome
- Multiple defects (OAT – oligoastheno-teratospermia)
  - r/o varicocele (usual cause)

## Chapter 43 Questions - Infertility.doc

- TRUS + SV aspiration: r/o partial ED obstruction
- Normal SA
  - perform PCT
    - abnormal = poor coital technique
    - normal: r/o ASA (in female and male)
      - ◆ no ASA = unexplained infertility → get sperm function testing: SPA or acrosome reaction test
        - ♦ normal → IVF/ICSI

### What is the DDx of infertility based on the following criteria:

- Low ejaculate volume
  - **retrograde ejaculation – anejaculation**
    - anatomic = BN destruction
      - ◆ congenital: extrophy/epispadias, prune belly syndrome
      - ◆ acquired: prostatectomy: TURP, radical, simple, TURBN
    - sympathetic denervation/failed emission
      - ◆ iatrogenic: RPLND or pelvic surgery
      - ◆ neurologic: SCI #1 overall cause of ejaculatory failure (also myelo, transverse myelitis, etc.), DM, MS
      - ◆ meds:
        - ♦ antihypertensives: ganglion blockers and alpha blocker
        - ♦ antidepressants
        - ♦ antipsychotics
        - ♦ antiandrogens
        - ♦ psychologic: inability to achieve orgasm
  - lack of SV contribution
    - ↓ production by SV or prostate: androgen deficiency
    - ejaculatory duct obstruction (SV → urethra)
      - ◆ congenital: vasal agenesis; usu. assoc. w/ SV agenesis, CF, UDT
      - ◆ acquired: intrinsic = infx/surgical e.g. RRP, extrinsic: cysts
  - spurious: collection problem: most common cause of ↓ volume in a nonazoospermic Pt
    - incomplete collection
    - short abstinence period
    - masturbation: volume may be ↓ vs. intercourse
- Azoospermia
  - evaluation geared towards distinguishing b/w obstructive and nonobstructive azoospermia
  - Pre-testicular (hypogonadotropic hypogonadism) = Endocrinopathy
    - Hypothalamic (hypogonadotropic hypogonadism): Idiopathic, Kallman's syndrome, Laurence-Moon-Bardet-Biedl, Prader-Willi (low GnRH)
    - Pituitary: Hyperprolactinemia, isolated LH deficiency (Fertile Eunuch Syndrome), Isolated FSH deficiency, Cushing's disease, adenoma (prolactin), radiation, hemorrhage, hypophysectomy, infarction, tumours, infectious
    - Other: adrenal (adrenal carcinoma, CAH), thyroid disease, androgen excess (exogenous = anabolic steroids/testosterone, Endogenous = CAH), Estrogen excess (Obesity, Adrenal tumours, Sertoli cell or Leydig cell tumours, Liver failure), Glucocorticoid excess
  - Testicular (hypergonadotropic hypogonadism) = spermatogenic failure
    - Congenital
      - ◆ chromosomal
        - ♦ Klinefelter's syndrome and chromatin –ve Klinefelter's syndrome
        - ♦ Maturation arrest: Idiopathic, Congenital = XYY syndrome, Varicocele
        - ♦ Y microdeletions
        - ♦ Noonan's syndrome, Down's syndrome, androgen insensitivity syndrome (X-linked recessive)
        - ♦ XX male
        - ♦ XYY syndrome
      - ◆ non-chromosomal
        - ♦ bilateral anorchia
        - ♦ vanishing testis
        - ♦ UDT, prune-belly
        - ♦ myotonic dystrophy
    - Acquired
      - ◆ heat: varicocele, hot tubs
      - ◆ trauma: torsion, surgery
      - ◆ tumours: bilateral testis ca
      - ◆ gonadotoxins: nitrofurantoin, sulfasalazine, CCB, chemo, rads, EtOH, cocaine, smoking
      - ◆ infectious: viral orchitis
      - ◆ vascular
      - ◆ SCO
      - ◆ idiopathic

## Chapter 43 Questions - Infertility.doc

- Post-testicular (disorder of sperm delivery)
  - Non-Obstructive: Idiopathic
    - ◆ retrograde ejaculation – anejaculation
      - anatomic = BN destruction
        - congenital: extrophy/epispadias, prune belly syndrome
        - acquired: prostatectomy: TURP, radical, simple, TURBN
      - Ejaculatory failure: sympathetic denervation/failed emission
        - iatrogenic: RPLND or pelvic surgery
        - neurologic: SCI #1 overall cause of ejaculatory failure (also myelo, transverse myelitis, etc.), DM, MS, neurotoxic drugs, spina bifida
        - meds: antihypertensives: ganglion blockers and alpha blockers, antidepressants, antipsychotics, antiandrogens
        - psychologic: inability to achieve orgasm
    - ◆ lack of SV contribution
      - ↓ production by SV or prostate: androgen deficiency
      - ejaculatory duct obstruction (SV → urethra)
        - congenital: vasal agenesis; usu. assoc. w/ SV agenesis, CF, UDT
        - acquired: intrinsic = infx/surgical e.g. RRP, extrinsic: cysts
    - ◆ spurious: collection problem: most common cause of ↓ volume in a nonazoospermic Pt
      - incomplete collection, short abstinence period, masturbation: volume may be ↓ vs. intercourse
  - Obstructive
    - ◆ Ejaculatory duct obstruction (ejaculatory duct cyst, utricle cyst)
    - ◆ Vasal obstruction: Vasectomy, vasal injury with hernia repair or orchidopexy, CF, CBAVD, infection (TB, smallpox)
    - ◆ Epididymal obstruction (CF, TB, smallpox, epididymitis, Young's syndrome)
- Oligoasthenoteratospermia
  - varicocele, cryptorchidism, idiopathic, drugs (alcohol, smoking, caffeine, cocaine, nitrofurantoin, cimetidine), heat, toxins, systemic infection, endocrinopathy
- Normal SA
  - gyne abnormality, abnormal coitus, acrosomal defects, ASA, unexplained
- Asthenospermia
  - Physiological - prolonged abstinence
  - Idiopathic
  - Congenital structural abnormality in sperm – all lead to dyskinetic sperm because of defective propulsion mechanism
    - Kartagener's (lack of inner dynein arm in axoneme of flagella), Immotile cilia, Defects in the outer dense fibres of sperm
  - Infection
    - GU tract: STD, epididymitis, postatitis (esp. chronic prostatitis),
    - Recent febrile illness (viral or bacterial)
  - Immunological
    - ASA: (ductal obstruction, epididymitis, cryptoorchidism, varicocele, orchitis, torsion, trauma, testicular biopsy) decrease sperm motility
  - Lubrication: K-Y jelly, Keri-lotion, Surgilube and saliva decr sperm motility
  - Environmental - hot tubs/sauna: high temperatures impair sperm motility
  - Post vasectomy reversal - development of antisperm antibody impairs sperm motility
  - Varicocele
  - Prolonged transport time

### What is the distribution of pts presenting w/ infertility by findings on SA?

- Normal SA: 14%
- Azoospermia: 14%
- Multiple abnormalities/OAT: 49%
- Oligospermia: 4%
- Asthenospermia: 6%
- Teratospermia: 4%
- Low volume: 7%
- Pyospermia: 2%

### What is the distribution of pts by diagnostic category after full evaluation?

- varicocele: 38%
- idiopathic: 23%
- obstruction: 13%
- normal: 9%



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- cryptorchidism: 3%
- testicular failure: 3%
- ASA, ejaculatory dysfunction, gonadotoxin: 2% each
- endocrinopathy, pyospermia: 1% each
- genetic (includes CF), torsion, ED, testis ca, ultrastructural, viral orchitis, systemic illness, hypospadias: <1% each

### What disorders/events have been associated w/ development of ASA?

- anything that may disrupt the blood-testis barrier
  - Probable
    - vasectomy: occurs in 60% of men after vasectomy
    - CBAVD: ASA present in 1/3
    - epididymitis
    - cryptorchidism
    - GU trauma
    - mumps orchitis
  - Possible
    - torsion: most studies have not demonstrated this
    - varicocele: evidence for and against
    - homosexual rectal intercourse
    - STDs
    - testicular cancer
    - hx of testicular biopsy

### What assays have been used to detect ASA, and what are the advantages and disadvantages of each?

- Direct assays: detect present of ASA on pts sperm → scoring based on % of motile sperm w/ bead/RBC binding
  - Mixed antiglobulin reaction (MAR): use anti-human Ig coated RBC to bind to sperm
    - quick, uses unwashed specimen, determines % of sperm coated w/ Ig
    - only detects IgG, titer not determined
  - Sperm MAR: use anti-human Ig coated latex particles to bind to sperm
    - quick, uses unwashed specimen, determines % of sperm coated w/ Ig
    - only detects IgG, titer not determined
  - Immunobead test: uses anti-human Ig coated polyacrylamide beads to bind to sperm
    - can detect all Ig and location of Ig on sperm, as well as % of sperm coated
    - must wash sperm, titer not determined
- Indirect assays: measure ASA in pts blood → require donor ASA-negative sperm
  - Tray agglutination test (TAT) or Gelatin agglutination test (GAT): measure sperm agglutination
    - determine titer, but does not determine Ig class or % of Ab on sperm surface
  - Sperm immobilization test (SIT): measures sperm immobilization
    - determines titer, but only detects complement fixing Ig
  - ELISA
    - can determine quantity and class of Ig, but uses fixed sperm (exposes clinically irrelevant Ag)

### How do ASA affect sperm function?

- cervical mucus penetration impaired
- inhibition of sperm capacitation
- premature induction of acrosome reaction
- impairment of zona binding
- impairment of ova fertilization

### What is the incidence of ASA?

- present in 10% of men presenting w/ male infertility
  - < 2% of fertile population

### What is the management of pts w/ pyospermia?

- WBC staining to confirm pyospermia vs. elevated # of immature germ cells
- tx: NSAIDs, empirical antibiotic therapy, frequent ejaculation, prostatic massage, ART w/ semen processing to remove WBC

### Describe the technique of vasography.

- at scrotal vas via puncture or transverse vasotomy

### **Chapter 43 Questions - Infertility.doc**

- inject plain NS or NS+dye to document distal patency
- if NS does not pass easily, inject dilute nonionic contrast or pass 2-0 monofilament to determine site of obstruction  
→ N vasogram: contrast seen throughout length of vas, SV, ED, and bladder
- proximal patency to epididymis documented by microscopic visualization of sperm in intravasal fluid

### **What are the indications for TRUS in the infertile male?**

- azoospermic pts suspected of having ED obstruction
- oligospermic pts suspected of partial ED obstruction

### **What is the normal diameter of the SV on TRUS?**

- normal diameter of SV behind bladder is 1.5cm  
→ some pts w/ obstructed SVs are not dilated → may need to do SV aspiration or vasography

### **What are the clinical findings associated w/ partial ED obstruction?**

- normal/low-normal semen volume
- decreased motility
- early demise of sperm in vitro in pts w/ normal hormones and normal volume testes

### **Describe the technique of venography for the infertile male.**

- used to detect and treat varicoceles  
→ Seldinger technique through R femoral or internal jugular venous approach  
→ pt in reverse Trendelenberg  
→ catheter tip just inside renal vein
- false +ve seen if ++ pressures used to inject contrast or if vein cannulated
- used only for pts w/ suspected recurrence after varicocele repair

### **What is the role of scrotal and abdominal US in the infertile male?**

- Scrotal US  
→ used for diagnosis of varicoceles → do not use if physical exam is normal  
➢ also used to diagnose testicular mass  
→ initial criteria: numerous large veins > 3mm + reversal of blood flow w/ Valsalva  
→ accuracy only 60% compared to physical exam + venography
- Abdo US  
→ used to assess kidneys in pts w/ abnormal vas  
→ ipsilateral renal anomalies in 80% men w/ UAVD → most common: renal agenesis

### **What is defined as a normal post-coital test?**

- no agreement as to how the test should be performed, timing of test, or grading system  
→ normal usually defined as > 10-20 sperm seen / HPF  
→ progressive motility should be seen in most sperm
- in vitro cervical mucus tests developed to standardize cervical mucus interaction  
→ drop of sperm placed next to cervical mucus under microscope  
→ ability of sperm to penetrate mucus examined microscopically: measure migration distance, penetration density, quality of movement  
→ nonreproduceable, not quantifiable
- with normal PCT, cervical factor or semen deposition abnormality not involved

### **What are the potential causes of an abnormal PCT?**

- inappropriate timing of PCT
- anatomic abnormalities
- semen or cervical mucus ASA
- inappropriately performed intercourse
- abnormal semen

### **What are the indications for the PCT?**

- hyperviscous semen
- unexplained infertility
- low-volume or high-volume semen specimens w/ normal total sperm counts  
→ not necessary to perform PCT in men w/ poor quality SA → all will have poor PCT

## Chapter 43 Questions - Infertility.doc

### How does one perform cross-mucus hostility testing?

- woman's mucus placed in contact w/ donor sperm and partner's sperm
- donor mucus placed in contact w/ donor sperm and partner's sperm

### How does one test for the acrosome reaction?

- sperm must undergo capacitation prior to acrosome reaction → takes 3hrs in vitro (4-6hrs in vivo)
- sperm induced to undergo acrosome reaction post-capacitation by exposing to acrosome-inducing agents
- normal: spontaneous acrosome reaction rate of < 5%, induced rate of 15-40%
- abnormal: high spontaneity, low induceability

### How does one perform the sperm penetration assay?

- zona pellucida removed from hamster ova (normally prevents cross-species fertilization)
- determine % of ova that have been penetrated or by calculating # of sperm that have penetrated each ovum
- normal: sperm penetrate 10-30% of ova
- not standardized
- perform only in men w/ low # of morphologically normal sperm → r/o fertilization defect

### How does one perform the hemizona assay?

- human zona pellucida divided in half, each half incubated w/ donor sperm or pt sperm
- hemizona index = # pt sperm bound / # donor sperm bound
- normal > 0.6

### How can one perform sperm viability assays?

- eosin Y and tryptophan blue staining
  - dyes penetrate dead sperm, excluded from live sperm w/ intact cell membranes
- hypo-osmotic sperm-swelling test
  - live sperm w/ intact membranes will be able to maintain an osmotic gradient
  - if placed in hypo-osmotic solution, water flows into viable cells, causing tails to bulge
    - viable sperm identified may be chosen for use during ICSI
  - non-viable sperm do not maintain a gradient → do not bulge

### What % of infertile men have chromosomal abnormalities seen on testing?

- karyotype abnormalities seen in:
  - 6% of all infertile men
  - 10-15% of azoospermic men
  - 4-5% of oligospermic men
  - 1% of normospermic men
- Y chromosome microdeletions seen in:
  - 7% of all infertile men
  - 13% of azoospermic men
  - 3-7% of oligospermic men
- 0.4% in newborns (baseline)

### What are the indications for testicular biopsy?

- in azoospermic men to differentiate b/w obstructive and non-obstructive azoospermia
  - if discrepant testis volumes, perform on larger testis only
- in pts w/ non-obstructive azoospermia to retrieve sperm for ICSI + cryopreservation
- r/o partial ductal obstruction in pts w/ severe oligospermia, normal sized testes, and normal FSH
  - **testis bx not indicated in other pts w/ oligospermia**

### What are the different histologic patterns seen on testis biopsy?

- Normal testis
  - seminiferous tubules seen separated by thin layer of loose interstitium w/ Leydig cells, blood vessels, lymphatics, CT
  - Sertoli cells + spermatogonia lining BM
  - germ cells seen in all steps of spermatogenesis seen within seminiferous tubules
- Hypospermatogenesis
  - reduction in number of all germinal elements
  - see thinner layers of germ cells within seminiferous tubules
  - organization of germinal epithelium may be interrupted, immature germ cells may be seen in lumen

### Chapter 43 Questions - Infertility.doc

- normal interstitium and Leydig cells
- most common patterns seen in infertile men: hypospermatogenesis and maturation arrest
- Maturation arrest
  - histologically see spermatogenesis proceeding normally until specific stage, at which point no further maturation of germ cells seen
  - arrest may be at: primary spermatocyte, secondary spermatocyte, or spermatid → block at consistent stage
  - either complete maturation arrest or partial maturation arrest
  - may see in combination w/ hypospermatogenesis
- Germinal aplasia (Sertoli cell only - SCO)
  - seminiferous tubules seen w/ Sertoli cells and complete absence of germ cells
  - diameter of seminiferous tubule reduced
  - normal interstitium, thick BM
  - small-to-normal sized testes w/ normal/elevated FSH levels
  - **no treatment available**
- End-stage testis
  - tubular and peritubular sclerosis and hyalinization
  - germ cells absent, Sertoli cells may or may not be present
  - Leydig cells absent or reduced in sclerotic interstitium, may be clumped
  - testes bilaterally atrophic and firm → ex: Klinefelter's
- Others
  - hypogonadotropic hypogonadism: seminiferous tubules very small → no germ cells or Leydig cells
  - isolated LH deficiency: normal spermatogenesis or hypospermatogenesis, decreased Leydig cell #
  - testicular atrophy: normal-sized seminiferous tubules w/ depletion of germ cells

### What are causes of azoospermia or oligospermia with a normal testis biopsy?

- True
  - Idiopathic
  - Congenital: Varicocele, seminiferous tubule ultra-structural abnormality, hyperabsorption of sperm by epididymis
  - Immune = ASA
  - Iatrogenic = XRT, chemo, gonadotoxins
  - Post-testicular problem (obstruction or ejaculatory failure)
- False: sampling error

### How can one classify causes of male infertility?

- Endocrine causes (Pre-testicular)
  - Hypothalamic
    - Isolated hypogonadotropic hypogonadism (Kallman's syndrome – Xlinked R)
    - Prader-Willi (low GnRH)
    - Laurence-Moon-Bardet-Biedl (AR)
  - Pituitary disease
    - pituitary surgery, infarction, tumours, rads, infectious disease
    - Fertile eunuch syndrome (isolated LH deficiency)
    - Isolated FSH deficiency
    - PRL excess (adenoma)
    - Cushings: Glucocorticoid excess
  - Androgen excess: endogenous, exogenous
  - Estrogen excess: obesity, adrenal tumours, Sertoli/Leydig tumours, liver failure
  - Adrenal/Thyroid abnormalities
  - Abnormalities of androgen action
    - deficiency of androgen synthesis
    - defect in T → DHT conversion (5αR deficiency)
    - defects in AR → 46XY male pseudohermaphrodism, X-linked recessive at Xq11-12
- Disorders of spermatogenesis (Testicular)
  - Chromosomal disorders
    - Klinefelter's
    - XX Male
    - XYY
    - Noonan's syndrome, Down's syndrome
    - Y chromosome microdeletions
  - Genetic: prune belly, myotonic dystrophy, AIS, Noonan's syndrome

### Chapter 43 Questions - Infertility.doc

- Congenital: cryptorchidism, intersex, bilateral anorchia, SCO syndrome
- Vanishing testis syndrome
- Testicular torsion
- Varicocele
- Orchitis
- Gonadotoxins
  - Chemo/radiation
  - Heat
  - Environmental toxins
  - Medications
- Idiopathic
- Disorders of sperm delivery (Post-testicular)
  - Ductal obstruction
    - ED obstruction: ejaculatory duct cyst, utricle cyst
    - Vasal obstruction: vasectomy, injury w/ hernia repair, CF, CBAVD, infection (TB, smallpox)
    - Epididymal obstruction: CF, TB, smallpox, epididymitis, Young's syndrome
  - Ejaculatory disorders
    - retrograde ejaculation: TURP, TURBN, DM, spina bifida, alpha blockers, neurotoxic drugs, MS
    - neurologic abnormalities: SCI, spina bifida, post-RPLND
- Sperm function disorders: immunologic disorders (ASA), ultrastructural abnormalities of sperm

### What are the symptoms and signs of pituitary disease?

- growth retardation, delayed puberty, adrenal/thyroid deficiency, ED, infertility, visual field changes, headaches
  - normal male secondary sexual characteristics if post-pubertally acquired pituitary disease
- small soft testes (vs. small firm testes for primary testicular failure/end-stage testes)
- plasma T low/low-normal, gonadotropins low or LH low/normal (hypogonadotropic hypogonadism)

### What is Kallman's syndrome?

- congenital hypogonadotropic hypogonadism
- genetically heterogeneous disorder, X-linked or AD or AR
- Symptoms
  - associated w/ anosmia, cryptorchidism, gynecomastia, other congenital anomalies (craniofacial asymmetry, cleft palate, color blindness, deafness, renal anomalies)
  - delay in pubertal development
  - length of arms and legs may be greater than trunk
  - prepubertal testes
    - if testes enlarged, pt has delayed puberty rather than hypogonadotropic hypogonadism
- Labs
  - LH pulses not present
- Treatment
  - androgen replacement w/ testosterone enanthate/cypionate 200mg IM q2weeks → virilization
  - gonadotropin therapy for spermatogenesis
    - hCG 2000 IU SC qMWF → initiates spermatogenesis
    - FSH: hMG (containing 75 IU LH and 75 IU FSH) or recombinant human FSH 75 IU → completion of spermatogenesis
  - GnRH therapy
    - intermittent SC injections via pump
    - only for pts w/ intact pituitary: dependent on pituitary secretion of FSH/LH
    - contraindicated in pts w/ acquired hypogonadotropic hypogonadism

### What is fertile eunuch syndrome?

- isolated LH deficiency
  - eunuchoid habitus, large testes, small-volume ejaculates
  - low plasma T, LH levels, normal FSH
  - testes biopsy: mature germinal epithelium, Leydig cells not apparent due to insufficient LH stimulation
  - enough intratesticular T made to support minimal spermatogenesis, but inadequate peripheral androgens for virilization

### What are the sx of isolated FSH deficiency?

- normal virilization, normal LH and T

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- oligospermia or azoospermia due to lack of FSH → tx w/ recombinant human FSH

### What is Prader-Willi syndrome?

- deletion of locus at 15q11-13
- sx: obesity, hypotonic musculature, mental retardation, small hands and feet, short stature, hypogonadism
- LH and FSH deficiency due to lack of GnRH secretion
- tx: same as Kallman's

### What is Laurence-Moon-Bardet-Biedl syndrome?

- syndrome of hypogonadotropic hypogonadism, retinitis pigmentosa, polydactyly, and hypomnesia

### What are the causes of androgen excess?

- exogenous sources
  - anabolic sources
- endogenous sources
  - metabolic abnormalities: CAH
    - 21-OHase most common cause
    - sx: short stature, precocious puberty, premature enlargement of penis w/ testes remaining small
    - treatment w/ steroids decreases ACTH production, decreasing adrenal androgen production
      - ◆ stimulates endogenous LH/FSH production and testicular steroidogenesis
  - androgen-producing tumour in testis or adrenal
    - **testes US in all pts w/ androgen excess**

### What are the sources of estrogen excess?

- estrogen-secreting tumours
- testicular Sertoli cell tumours
- interstitial Leydig cell tumours
- hepatic dysfunction
- obesity: peripheral adipose tissue has aromatase, which converts androgen

### What are the sx of estrogen excess?

- ED, gynecomastia, testicular atrophy

### What are the causes of PRL excess?

- pituitary tumour
- stress
- medications
- medical illness
  - renal failure
- idiopathic
- elevated TRH
- chest wall irritation
- thyroid dysfunction

### What are the sx of PRL excess?

- ED
- male infertility
- decreased LH/FSH, T → small % may have borderline normal T levels
- elevated PRL

### What is the tx of a PRL-secreting tumour?

- get MRI of pituitary w/ gadolinium contrast
- r/o hyperthyroidism
- medical therapy: most pts respond
  - bromocriptine
  - cabergoline: fewer s/e and less-frequent dosing
- surgery
- radiation

### How does glucocorticoid excess cause infertility?

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- may suppress LH secretion → causes androgen suppression and testicular dysfunction  
→ may be due to endogenous production (Cushing's) or exogenous (medical therapy)
- hypospermatogenesis and maturation arrest seen on biopsy

### How can androgen abnormalities cause infertility?

- defect in androgen synthesis
- deficiency in T conversion
- AR abnormalities  
→ cause AIS: 46XY male pseudohermaphroditism → have elevated T and LH, normal FSH

### What is Klinefelter's syndrome?

- XXY, due to non-disjunction of meiotic chromosomes of gametes  
→ nondisjunction during meiotic cell division of developing embryo leads to mosaicism
- Sx: phenotypic male w/ small firm testes, gynecomastia, delayed completion of puberty, ED, mental retardation, psychiatric disturbances, tall
- FSH levels ++ elevated, LH elevated or normal, T decreased in 50-60%  
→ up to 50% may have normal T, but gonadotropins usually elevated
- azoospermia on SA, seminiferous tubular sclerosis on testis biopsy
- diagnosis made on karyotype: 47XXY or 46XY/4XXY or more
- treatment of infertility: TESE + ICSI/IVF → not possible to improve spermatogenesis  
→ **50X increased risk of breast cancer**

### What is XX male syndrome?

- a.k.a. sex reversal syndrome
- Sx similar to Klinefelters: small firm testes, frequent gynecomastia, small/normal penis, azoospermia, +/- hypospadias
- seminiferous tubule sclerosis on testes biopsy → no sperm ever seen on TESE
- elevated gonadotropins
- 46XX on karyotype → some pts have SRY

### What is XYY syndrome?

- Sx: tall pts, severe oligospermia/azoospermia
- maturation arrest/complete germinal aplasia, seminiferous tubule sclerosis on testis biopsy
- gonadotropins and T usually normal
- occasional pt have been fertile

### What is Noonan's syndrome?

- gene defect on chromosome 12 → 46XY, phenotype similar to Turner's (45XO)  
→ short stature, hypertelorism, webbed neck, low-set ears, cubitus valgus, ptosis, cardiovascular abnormalities
- cryptorchidism, testicular atrophy, elevated gonadotropins
- no treatment

### How do Y chromosome microdeletions cause infertility?

- 3 nonoverlapping regions of long arm of Y chromosome associated w/ azoospermia or severe oligospermia
  - AZFa (proximal): least common
    - genes identified: USP9Y (a.k.a. DFFRY), DBY, UTY
  - AZFb (middle)
    - gene called RBMY (RNA-binding motif, Y chromosome) produces RNA-binding protein localized to germ cell nuclei
  - AZFd: 4<sup>th</sup> region b/w AZFb and AZFc → not well investigated
  - AZFc (distal): most common
    - deleted azoospermia gene (DAZ) responsible for spermatogenic defects here → produces RNA-binding protein
- most de novo: not inherited from parents
- pts phenotypically normal  
→ only abnormality is defect in spermatogenesis: 5-18% of men w/ oligo- or azoospermia have Y chromosome microdeletions  
→ pts w/ testicular failure: 1-37% have Y microdeletions
- no treatment to improve spermatogenesis → can use IVF/ICSI
- deletions will be transmitted to male offspring → need genetic counselling
- patterns to deletions:  
→ AZFa: SCOS

## Chapter 43 Questions - Infertility.doc

- AZFb: maturation arrest
- AZFc: hypospermatogenesis
- AZFd: disordered spermatogenesis

### What is vanishing testis syndrome?

- bilateral anorchia in genetic XY males → prepubertal male phenotypes
- testes lost in utero due to infection, vascular injury, testicular torsion
- tx: virilization w/ T at puberty, T supplementation for life
- no tx for infertility

### How does cryptorchidism cause infertility?

- oligospermia: counts  $< 12\text{-}20 \times 10^6/\text{ml}$  in 50% pts w/ bilateral cryptorchidism, 25% of pts w/ unilateral
- biopsy: decreased # of Leydig cells
- higher the cryptorchid testis, more severe the testicular dysfunction
  - no germ cells in 20-40% of inguinal testes, 90% of intra-abdominal testes
- fertility rates of 78-92% of surgically corrected unilateral cryptorchidism, 30-50% of bilateral

### Why are varicoceles more common on the L?

- L testicular vein drains directly into L renal vein
- absence of venous valves more common on L
- nutcracker phenomenon: L renal vein compressed b/w SMA and aorta → increased pressure in L testicular venous system

### How does a varicocele affect testicular function?

- increased temperature
  - raises intrascrotal temperature by  $0.6^\circ\text{C}$
- reflux of renal and adrenal metabolites
- decreased blood flow and hypoxia
- ? increased back pressure

### What are the common findings on SA in pts w/ varicoceles?

- decreased motility in 90%
- oligospermia  $< 20 \times 10^6/\text{ml}$  in 65%
- morphology: more than 15% tapered forms → "stress pattern"

### How does varicocele repair affect fertility and sperm parameters?

- causes catch-up growth in adolescents w/ smaller ipsilateral testes
- improves SA in 70%
  - improvement in motility most common: 70%
  - improved counts in 51%
  - improved morphology in 44%
- conception rates of 40-50%

### What are the indications for varicocele repair?

- clinically detectable varicocele w/ abnormal SA in an infertile couple
- symptomatic varicocele
- restricted growth in ipsilateral testis
- cosmesis

### What is Sertoli-cell only syndrome?

- histologic diagnosis of complete absence of germ cells
  - cause is multifactorial: Y chromosome microdeletions seen in some pts
- FSH often (but not always) increased, T and LH normal
- **sperm recovered on TESE in 50%**

### How does orchitis cause infertility?

- postpubertal mumps causes orchitis in 30%, bilateral in 10-30% of cases
- permanent testicular atrophy several **months to years after infection**
  - interstitial edema and monocyte invasion
  - atrophy of seminiferous tubules



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→ hypergonadotropic hypogonadism and gynecomastia

### How does myotonic dystrophy cause infertility?

- causes myotonia (delayed muscle relaxation after contraction)
  - pts also have cataracts, cardiac conduction defects, premature frontal baldness, mental retardation
  - AD transmission
- testicular atrophy in 80%
  - severe tubular sclerosis on biopsy, Leydig cells normal
- elevated FSH
- no treatment

### How do gonadotoxins cause infertility?

- Chemotherapy
  - most chemo agents adversely affect spermatogenesis
  - **alkylating agents and procarbazine cause most damage**
    - cyclophosphamide, chlorambucil, mustine
    - >90% azoospermia in cyclophosphamide regimens → may take up to 10yrs to recover
  - permanent sterility in 80-100% Hodgkin's pts tx w/ MOPP and COPP
    - pts w/ Hodgkin's have subfertility prior to chemo as well
  - testis cancer pts: pre-existing spermatogenic defects in 25%
    - Jarvi: 50% have abnormal SA (usually severe oligospermia)
  - cisplatin regimens: most pts become azoospermic, but most recover within 4 yrs
  - no increased risk of birth defects after chemo
    - bank sperm prior to chemo anyway: best way to preserve fertility
    - use contraception for 3-24mo after chemo
  - may offer testicular biopsy to r/o obstx: no real role for TESE, as usually have uniform destruction of seminiferous tubules
- Radiation
  - germinal epithelium very radiosensitive due to high rate of cell division
  - spermatids more resistant than spermatogonia or spermatocytes
  - Leydig cells very radioresistant: T levels usually OK
    - FSH levels increase
  - Sertoli cells most radioresistant
  - azoospermia seen w/ doses > 65 cGy
    - recovery 9-18mo (<100cGy) to 5yrs (400-600cGy)
  - recovery to baseline within 2 yrs after radiation for seminoma
    - fractionated radiotherapy likely more toxic than single dose
  - single dose
    - 0.1Gy: sperm alterations
    - 0.8 Gy: oligospermia
    - 0.8-2Gy: azoospermia, recovery 9-18 mo
    - 2-3 Gy: azoospermia, recovery 30mo
    - 4-6 Gy: azoospermia, recovery > 5yrs
  - 25% become permanently infertile
  - avoid conception for 2 yrs after rads
  - no increase in birth defects
- Heat
  - lower sperm count seen in pts w/ tight underwear
- Occupational exposure
  - lead, arsenic, hydrocarbons, cadmium, 2-bromopropane
- Meds
  - marijuana: decreased serum T, gynecomastia, decreased sperm counts
  - cocaine: decreased counts
  - DES: epididymal cysts, cryptorchidism, vasal abnormalities
  - nitrofurantoin: causes early maturation arrest at primary spermatocyte stage
  - sulfasalazine: reversible defects in sperm count
  - CCB: reversible defect in sperm
- Alcohol
  - testicular atrophy in chronic alcoholics
    - peritubular fibrosis, decrease in # of germ cells

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- decreased T
- ED and gynecomastia also seen
- Cigarettes
  - conflicting reports → most studies say no effect
- Caffeine
  - no direct effects

### What are the options for empirical medical treatment for infertility?

- GnRH
  - useful in Kallman's syndrome, not good for idiopathic infertility
- gonadotropins
  - not useful for pts w/o demonstrable hormonal abnormality
- clomiphene citrate and tamoxifen (antiestrogens)
  - increase pituitary gonadotropin secretion by blocking feedback inhibition, increasing LH/FSH levels
  - clomiphene 25mg PO OD
  - pregnancy rates < 30%
  - inexpensive and safe tx for idiopathic male infertility → use only < 3mo
- testolactone
  - aromatase inhibitor: similar effect as antiestrogen
    - blocks conversion of T → estradiol
  - expensive, not widely studied
- androgens
  - lowers concentration of T in testis, decreases spermatogenesis → has contraceptive effect in men
  - **never use in infertility**
  - may be a long term effect (10-15%)
- vitamins
- anti-inflammatories
- testosterone-rebound therapy
  - **should not be used: currently no role → may cause permanent azoospermia**
  - large doses of exogenous T, administered parenterally to suppress activity of pituitary
  - suppression of LH release decreases intratesticular level of T
  - androgen therapy stopped in hope that system will rebound and improve spermatogenesis

### What are the causes of ductal obstruction?

- Congenital: malformation, absence of ductal structures (CBAVD)
  - CBAVD most common causes of obstructive azoospermia in pts w/o vasectomy
- Acquired: infection, stricture, vasectomy

### What are the common findings in pts w/ CBAVD?

- presence of caput epididymis w/o remainder of epididymis or vas
- absent/hypoplastic SVs
- unilateral renal agenesis
- low-volume azoospermic ejaculates: acidic, fructose-negative
- normal spermatogenesis on testis biopsy

### What are the causes of ejaculatory dysfunction?

- Anatomic
  - retrograde ejaculation
  - bladder neck surgery, TURP
- Functional
  - neurologic abnormalities: DM, MS, retroperitoneal surgery

### What is the treatment for ejaculatory dysfunction?

- Medical therapy
  - not useful for pts w/ TURP or TURBN
  - pseudoephedrine 60mg PO QID, ephedrine 25-50mg PO QID, imipramine 25mg BID
  - induces ejaculation due to increased tone of BN sphincter
- recovery of sperm + IUI
  - optimize urine pH and osmolarity for sperm survival: Na bicarb 650mg PO QID, acetazolamide 250mg PO QID, or baking soda (2 tsp night before and 2hrs before ejaculation)

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- sperm recovered by centrifugation and washing
- penile vibratory stimulation
  - ejaculation in 70% of SCI men
  - used in pts w/ UMN lesion above T10: LMN lesions not likely to respond
- electroejaculation
  - pulsed electrical current applied to periprostatic plexus w/ rectal probe
  - ejaculation in 75% of men
  - only use in men that are not candidates for or who have failed penile vibratory stimulation
  - autonomic dysreflexia in pts w/ complete lesion above T4-6 → pretreat w/ 10mg SL nifedipine

### What is the treatment for immunologic infertility?

- steroids: attempt to suppress ASA formation
  - uncontrolled studies: 30-40% pregnancy rates
  - intermediate dose cyclical regimen
- sperm processing
  - chymotrypsin to digest off Fc portion of ASA off sperm: improves sperm motility and decrease agglutination
  - IVF/ICSI: decreased fertilization rates w/ ++ ASA

### How do ultrastructural abnormalities of sperm affect fertility?

- defects in outer dense fibers
  - less common than microtubular defects
  - causes dyskinetic sperm w/ flagellar movements that are not normal
  - round headed sperm w/ absence of acrosome seen
    - Type I: complete absence of acrosome and acrosomal contents
    - Type II: remnants of acrosome seen, some ability to fertilize ova
- defects in microtubules
  - most common: aberration from standard 9+2 microtubule organization
  - **complete absence of inner and outer dynein arms**
  - combined w/ respiratory tract defects = immotile cilia syndrome or primary ciliary dyskinesia
  - combined w/ situs inversus = Kartagener's syndrome
- defects in mitochondria
- abnormalities of connecting piece
  - separation of head from tail

### What are the options for assisted reproductive techniques?

- Semen processing
  - sperm washing, swim-ups (pelleted sperm swim up into supernatant), sedimentation, and centrifugation
- IUI
  - inject processed sperm through cervix into uterine cavity
  - bypasses cervical mucus
  - **do not inject unprocessed semen**: seminal PGs may cause severe uterine cramping, pelvic infection
  - natural cycle IUI (women ovulate naturally) vs. induction of maturation of multiple ova (superovulation)
    - poor results of natural-cycle infertility in male factor infertility (pregnancy rates 1-3% per cycle)
    - ovulation induction w/ clomiphene citrate (pregnancy rates of 5-8% per cycle) or injectable gonadotropins (pregnancy rates 10-15% per cycle)
    - most pregnancies in 1<sup>st</sup> 3 cycles
  - poor results if inject sperm w/ counts < 1 million after processing
    - need pre-processing SA counts of 5-10 million sperm total
- IVF
  - most centers use gonadotropin superovulation
  - developing embryos incubated for 2-3d in culture, then transferred transcervically into uterus
    - some cultured for 5d, transferred at blastocyst stage → allows for transfer of fewer embryos
  - 20-30% of embryos implant
  - clinical pregnancy rate of 20-30% per cycle
  - pregnancy rate of 36% for < 35yrs, 13% for > 40yrs
  - live birth rate of 31% for < 35yrs, 7.6% for > 40 yrs
- Sperm retrieval
  - MESA: retrieve sperm out of ductal system in CBAVD
  - PESA: less invasive, but fewer sperm aspirated, more procedures needed for subsequent cycles
  - TESE

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- IVF/ICSI
  - increase in sex chromosomal abnormalities in kids born from ICSI cycles
  - increase in major congenital malformation rates, decreased cognitive development

### What are the indications for IUI?

- male factor infertility
- unexplained infertility
- cervical mucus abnormalities
- anatomic abnormalities interfering w/ deposition of sperm at cervical os
  - severe hypospadias
  - retrograde ejaculation
  - ED
- cervical factor infertility
- anatomic abnormalities interfering w/ intercourse
  - dyspareunia
- psychogenic sexual dysfunction

### What are the complications of IUI?

- cramping
- pelvic infection: < 0.5%
- allergic reactions: rare
- multiple gestations: 15-30%
- HIV

### MCQs

Etiology of infertility in DM includes: retrograde ejaculation

Kartagener's syndrome is a defect of **inner** dynein arm

### What are the AUA Guidelines for evaluation of the infertile male?

- Initial screening evaluation: if no pregnancy in 1 yr of unprotected sex, known male infertility risk, or known female factor exists
  - reproductive hx: coital frequency/timing, duration of infertility, childhood illnesses/development, systemic medical disease, sexual hx, STD hx, gonadal toxins/heat
  - 2 semen analyses
- Full evaluation: if initial screen abnormal, unexplained infertility, or infertility w/ treated female factor
  - reproductive hx: coital frequency/timing, duration of infertility, childhood illnesses/development, systemic medical disease, sexual hx, STD hx, gonadal toxins/heat
  - Px: ext. genitalia, secondary sexual characteristics, DRE
  - 2 SA
  - other tests as needed
    - Endocrine eval: if count < 10million/ml, impaired sexual fn, or findings suggesting endocrinopathy
      - ◆ FSH, T
    - Post-ejaculatory UA: if ejaculate volume < 1cc, unless pt has CBAVD or true clinical hypogonadism
      - ◆ any sperm in UA = retrograde ejaculation
    - TRUS: to identify ED obstruction w/ azoospermia, palpable vas, and ejaculate volume < 1cc
    - scrotal US: if Px inconclusive
    - genetics: if non-obstructive azoospermia and severe oligo (count < 5-10million) → prior to ICSI
      - ◆ CFTR gene: if CBAVD
      - ◆ karyotype
      - ◆ Y-chromosome microdeletions
      - ◆ genetic counselling
    - other tests: semen WBC, sperm Ab tests, sperm viability test, sperm-cervical mucus interaction tests, zona-free hamster oocyte tests, CASA
- Evaluation of azoospermia
  - CBAVD/UAVD: get abdo US to r/o renal agenesis
  - consider TRUS (in UAVD) to r/o segmental atresia
  - bilateral testicular atrophy
    - + high FSH and normal/low T: genetic testing
    - + low FSH, bilaterally small testes, and low T: serum PRL and pituitary gland imaging to r/o pituitary tumour
  - ductal obstruction w/ normal ejaculate volume, no atrophy, 1-2 palpable vas

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- normal FSH: get testicular bx to r/o obstructive azoospermia
- increased FSH (2X normal): testis bx only to retrieve sperm for ICSI
- low ejaculate volume and palpable vasa
  - TRUS to r/o obstruction
  - testis bx to r/o obstruction
  - vasography only at time of reconstruction
- Management of obstructive azoospermia
  - surgery: VV/VE, TURED, or IVF/ICSI
  - VV/VE preferable to ICSI in men w/ previous vasectomy if < 15 yrs previous and no female factors
  - TURED if obstruction at level of prostate
  - IVF/ICSI if:
    - advanced female age
    - female factors require IVF/ICSI
    - chance for success w/ ICSI > chance w/ VV/VE
    - cost to pt favours this approach
- Management of varicoceles
  - indications
    - palpable varicocele, documented infertility, female normal/correctable infertility, abnormal SA or sperm function tests
    - palpable varicocele and abnormal SA but not currently trying to conceive
    - adolescents w/ decreased testis size
  - monitoring in:
    - young men w/ normal SA → repeat SA q2y
    - adolescents w/ normal testis size
  - SA q3mo for 1 yr or until pregnancy
  - consider IUI and ART if infertility persists after successful varicocele repair





## **Chapter 44**

### **• Surgical Management of Male Infertility and Other Scrotal Disorders •**

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#### **What are the indications for testicular biopsy?**

- azoospermic men w/ normal size testes, palpable vasa, normal serum FSH levels
  - perform in men regardless of FSH levels and testicular volumes
  - usually perform bilaterally regardless of size

#### **Describe the technique of testicular biopsy.**

- local anaesthesia w/ cord block
  - GA/spinal if previous OR w/ scar or adhesions
- stretch skin over testis
  - ensure epididymis is posterior
- bilateral transverse 1cm scrotal incisions
  - alternative: midline incision
- dissect through skin/dartos
- deliver testis if anatomy distorted
- identify spot on testis free of vessels
- 4mm incision w/ microknife
- cauterize small vessels w/ bipolar
  - avoid tissue trauma
- specimen deposited into Bouin's, Zenker's, or collidine buffered glutaraldehyde
  - do not use formalin
- touch-prep: examine under light microscope for assessment of motility
- 2<sup>nd</sup> squash-prep if needed if no sperm seen
- close tunica albuginea w/ 2-3 interrupted sutures of 6-0 nylon
- close vaginalis w/ 5-0 Vicryl
- close skin w/ 5-0 monocryl

#### **What are the complications of testicular biopsy?**

- Intraop
  - damage to testicular artery during cord block: 5%
  - inadvertent biopsy of epididymis/vas/cord
    - certain obstruction of epididymis
    - if no sperm seen on biopsy w/ epididymis, obstruction is further proximal → no harm done
  - inadequate tissue sampling
  - improper placement into formalin: must be Zenker's or Bouin
- Post-op
  - bleeding/hematoma: most common
  - infection: rare due to rich blood supply of scrotum → no need for antibiotics
  - chronic orchalgia

#### **What are the contraindications of percutaneous testicular biopsy?**

- previous surgery resulting in scarring and obliteration of normal anatomy
  - injury to epididymis or testicular artery

#### **What are the indications for vasography?**

- Absolute
  - azoospermia, plus:
    - **complete spermatogenesis** w/ many mature sperm on biopsy
    - at least one **palpable vas**
  - perform only at time of reconstruction
- Relative

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- severe oligospermia w/ normal testis biopsy
- high-level of ASA that may be due to obstruction
- low semen volume and very poor motility (partial ED obstruction)

### What questions should vasography answer?

- are there sperm in the vasal fluid?
- is the vas obstructed?

### What are the different findings in vasal fluid often encountered at vasography?

- no sperm seen in vasal fluid
  - obstruction more proximal to vasal site examined
  - **usually epididymal obstruction**
- copious vasal fluid + many sperm
  - vasal or ED obstruction
  - vasography performed to find exact site
- copious thick white fluid w/o sperm
  - secondary epididymal obstruction + primary vasal or ED obstruction

### Describe the technique of vasography.

- testis delivered through a high vertical scrotal incision
- vas identified
- incise vasal sheath longitudinally to preserve vasal vessels
- deliver vas
- hemitranssect vas
- take fluid, place on slide and mix w/ drop of NS, seal w/ coverslip
  - examine for sperm, send for cryo
  - milk epididymis if no sperm seen and repeat
  - if no sperm seen → epididymal obstruction present
- cannulate distal end of vas w/ 24G angiocatheter sheath, inject 1cc RL to confirm patency
  - can inject 1cc dilute indigo carmine for further confirmation → urine should be blue/green
  - **do not use methylene blue → kills sperm, useless for IVF/ICSI or cryo**
- Findings
  - if motile sperm found, barbotage proximal end w/ 0.2cc tubal fluid media, process for cryo
  - if copious volume + sperm, obstruction near SV
    - pass 2-0 Prolene to delineate distal location of obstruction
    - formal vasography
    - #3 whistle tip catheter in vas
    - 16F foley in bladder: place on gentle traction to prevent reflux into bladder (obscures detail)
  - if obstruction at ED, inject indigo carmine to facilitate TURED
  - if vasography shows blind ending vas (congenital partial absence of vas), test for CF
  - if no sperm and vas patent, perform V-E
  - if ++ sperm and patent vas, retrograde ejaculation, lack of emission, or aperistalsis of the vas
- close hemitranssected vas w/ 2-3 interrupted 10-0 nylon and 9-0 nylon in 2 layers
- optional method: fine-needle vasography
  - expose vas in straight portion, use 30G lymphangiogram needle
  - difficult technique

### What are the complications of vasography?

- stricture
  - may be due to non-water soluble contrast
- injury to vasal blood vessels
- hematoma
  - use bipolar cautery for meticulous hemostasis
- sperm granuloma
  - due to leaky closure of vasography → can lead to stricture/obstruction

### What are the indications for transrectal vasography and SVography?

- TRUS w/ dilated SV or midline mullerian duct cyst w/ obstructive azoospermia

### How does one manage a pt w/ ED obstruction and secondary epididymal obstruction?



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- epididymal sperm aspiration for cryo + IVF/ICSI  
→ **simultaneous TURED + V-E rarely successful**

### Describe the technique of vasectomy.

- Preop
  - Hx: age, contraception, kids (current and previous, plans for future), discussed w/ partner, alternatives, does not protect against STDs, consider irreversible, PMHx, Meds, Allergies, FHx, Bleeding diathesis (ASA, anticoagulants)
  - Px: testicular volume, consistency, vas readily palpable, scrotal skin thickness
- Anaesthesia
  - valium 10mg PO 1 hr prior
  - 3-finger technique for vasal nerve block: grasp R vas w/ L hand, raise wheal w/ 1% plain xylocaine, advance in perivasal sheath, inject 2-5cc around vas
  - inject away from vasectomy site
- Conventional incision
  - mobilize vas to superficial site under scrotal skin, fix w/ either finger, towel clip, or needle
  - 1cm bilateral transverse incision or single median raphe incision
  - expose vas, deliver vas, occlude
  - leave incisions open to prevent hematoma formation
- No-scalpel vasectomy
  - vas fixed under median raphe, grasp w/ ring-tipped fixation clamp
  - sharp pointed curved mosquito hemostat used to puncture scrotal skin w/ 1 blade
    - skin punctured 1<sup>st</sup> w/ snap and spread to visualize vas if scrotal wall very thick
  - vas wall skewered w/ mosquito and turned 180°, lifting vas out
  - vessels cleared away from vas
  - vas divided, occluded, transected
  - pinch hole for 1min for bleeding
- Percutaneous vasectomy
  - chemical occlusion w/ cyanoacrylate and phenol
  - inject Congo red into R vas, methylene blue into L vas
    - pt voids at end of OR, urine should be brown: if red, L side missed, if blue, R side missed
- High-frequency US vasectomy
- Open-ended vasectomy
  - failure rate 4% if bury/seal abdominal end of vas
- Post-op
  - counsel: rest for 24-48h, ride home, back to work in 3-5d, no sex for 1-2 weeks, contraception until 2 -ve SA, no change in orgasm, etc.
  - SA x 2, 4-6 weeks apart, at about 3-4mo
  - if any motile sperm seen 3mo after vasectomy, repeat procedure

### What are the techniques of vasal occlusion?

- suture ligation
  - may cause necrosis and sloughing of cut end distal to tie, w/ sperm granuloma
  - failure rate 1-5% if ties alone
- 2 medium hemoclips on each end
  - less sloughing due to even pressure
  - failure rate <1% if clips alone
- intraluminal occlusion w/ needle electrocautery
  - cauterize 1cm in both directions
  - failure rate <0.5%
- interposition of fascia b/w cut ends
- folding back of vasal ends
- securing one end in dartos muscle
- **preferred method: remove 1cm segment + intraluminal cautery + hemoclip on each end**

### What are the advantages of NSV?

- less hematoma, infection, pain
- 40% shorter OR time

### What are the advantages of open-ended vasectomy?

- leakage of sperm at vasectomy site prevents pressure induced damage of epididymis

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- increases chance of successful reversal

### What are the complications of vasectomy?

- Intra-op
  - failure to find vas
  - injury to cord
- Short-term
  - hematoma: most common complication (2%)
    - higher rates if perform <10 vasectomies per year
  - infection (3.4%)
  - sperm granuloma
    - intense inflammatory reaction, due to high antigenicity of sperm
    - rarely symptomatic, increases chance of vasectomy reversal
  - pain
    - chronic pain: excise and occlude vasa w/ cautery (usually works)
    - congestive epididymitis: perform open-ended vasectomy to produce pressure-relieving granuloma
  - pregnancy: failure to use contraception
- Long-term
  - vasitis nodosa
  - chronic testicular/epididymal pain
    - 1/1000 pts
    - consider vasectomy reversal or open-ended vasectomy
    - if localized to epididymis, total epididymovasectomy relieves pain in 95%
  - alteration in testicular function
  - ASA production
    - occurs in 60-80% of men
  - chronic epididymal obstruction
  - increased atherosclerosis: in 1 study
  - increased prostate cancer: 1 study, but 2 larger scale studies after showed no link (?detection bias)
  - failure: 1/500

### Describe the technique of vasovasostomy.

- Pre-op
  - Hx: prior hx of natural fertility
  - Px
    - testis: small/soft testis = impaired spermatogenesis, poor outcome
    - epididymis: indurated/irregular = secondary obstruction, may require V-E
    - hydrocele: may be secondary obstruction, may require V-E
    - sperm granuloma: leakage at site, improved outcome
    - vasal gap: large gap may require inguinal exploration to mobilize vas
    - scars from previous OR: inguinal/scrotal scars = possible iatrogenic vasal/epididymal obstruction
    - varicocele
      - ◆ varicocele repair destroys all venous return in cord, only venous return left is along vas
      - ◆ if present, is safer to perform V-V/V-E first, then do varicocele repair 6mo later after venous/arterial channels have formed across anast
  - Labs
    - SA: examine for sperm in spun pellet → favourable prognosis
    - ASA (optional)
    - FSH: if small soft testis, measure FSH → elevated FSH = poor spermatogenesis, poor outcome
    - PSA: for all men > 40y
- Anaesthesia
  - light GA
- Procedure
  - Incision
    - scrotal incision: bilateral high scrotal incisions 1cm lateral to penile base: can extend toward external ring
      - ◆ deliver testis w/ tunica vaginalis left intact
    - inguinal incision: preferred if inguinal obstruction due to hernia or orchidopexy
      - ◆ incise through old scar
  - Vasal preparation
    - grasp vas above and below site of obstruction w/ 2 Babcock clamps

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- transilluminate periaidventitial sheath to prevent damage to vasal vessels
- mobilize vas to allow tension-free anast
- do not strip vas of sheath
- dissect out obstructed segment, excise w/ sperm granuloma if present
- blunt dissection of vas to external or internal ring if needed
- dissect testicular end of vas and transect
  - ◆ should be healthy, white, springy: if gritty, indicates scar → recut
- dilate lumen
- milk epididymis, examine fluid to confirm sperm
- NS vasogram to confirm patency
  - ◆ if not patent, pass 2-0 nylon to determine site of obstruction
  - ◆ if obstruction within 5cm of site, dissect out abdominal end
  - ◆ if 2<sup>nd</sup> obstruction too far away, consider crossed V-V
- use approximating clamp to remove all tension
- Anastomosis
  - operating microscope used, support arms
  - 6 double-armed sutures for inside-out placement of sutures
  - stain lumen w/ indigo carmine to visualize mucosa
  - dilate abdominal lumen if needed
  - 3 10-0 sutures placed anteriorly, 2 9-0 sutures placed as superficial layer
  - vas rotated 180°, 3 more 10-0 sutures placed
  - before last mucosal suture tied, irrigate lumen w/ RL to prevent clot formation
  - place 4 more 9-0 superficial nylons, 6 9-0 nylons as adventitial layer
  - approximate vasal sheath w/ 6 7-0 PDS sutures
- Wound closure
  - Penrose if extensive vasal dissection
  - close dartos w/ 4-0 absorbable
  - close skin w/ 5-0 monocryl
- Post-op
  - scrotal support x 6/52, no antibiotics needed
  - no sex, sports x 4 weeks
  - SA at 1, 3, 6 mo
  - redo V-V/V-E if azoospermia at 6mo

### What are the possible maneuvers to gain additional vasal length?

- separate cord structures from vas
- blunt finger dissection through external ring to free vas to internal ring
- dissect entire convoluted vas off attachments to epididymal tunica: gains 4-8cm
- transposition of testis if crossed V-V:

### What is the relationship b/w gross appearance of vasal fluid and microscopic findings?

- copious clear watery fluid = no sperm → V-V
  - usually get sperm later
- copious cloudy watery fluid = usually sperm w/ tails present → V-V
- copious creamy yellow water soluble fluid = many sperm heads, occasional whole sperm → V-V
- copious thick white toothpaste = no sperm → V-E
- scant white thin fluid = no sperm → V-E
  - only 15% of men w/ no sperm after barbotage have sperm after V-V
- scant fluid + granuloma, sperm on barbitage → V-V
- dry vas = no sperm → V-E

### What are the surgical principles to be followed for V-V?

- accurate mucosa-mucosa apposition
  - testicular side usually larger
- leakproof anast
  - vasal and epididymal fluid has no clotting factors or platelets, dependent entirely on sutures
- tension-free anast
- good blood supply
  - cut vas until healthy tissue
- healthy mucosa and muscularis

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- good atraumatic anast

### What are the indications for crossed V-V?

- unilateral inguinal obstruction w/ contralateral atrophic testis
- unilateral inguinal obstruction w/ contralateral epididymal obstruction

### What are the complications of V-V?

- similar to vasectomy: pain, infection, hematoma, granuloma, late stricture/obstruction

### What are the results after V-V?

- if sperm seen at time of V-V, SA +ve at 6 mo in 99.5%
- late obstruction in 12% by 14mo postop
- pregnancy in 53% by 2y

### What are the indications for epididymectomy?

- chronic infection/abscess of epididymis unresponsive to antibiotics
- CMV of epididymis in HIV+ men
- chronic unremitting pain after vasectomy

### Describe the technique of epididymectomy.

- vertical median raphe incision
- isolate vas at junction of straight and convoluted portions and transected
- dissect convoluted vas free from epididymal tunic to vasoepididymal junction
- open tunica vaginalis
  - avoid spermatic cord vessels
- ligate efferent ductules w/ absorbable suture, remove epididymis
- oversew edges of tunica vaginalis
- close dartos, skin

### What are the indications for spermatocelectomy?

- rarely indicated
  - unremitting pain
  - extremely large

### Describe the technique of spermatocelectomy.

- testis delivered, open tunica vaginalis
- spermatocele dissected free of epididymis
  - use OR microscope to prevent injury to epididymal tubules
- ligate attachment w/ 6-0 nylon
- reapproximate tunica vaginalis w/ 5-0 Vicryl
- close dartos, skin

### What is the Chevassu maneuver?

- exploration and occlusion of the testicular vessels before biopsy of suspicious lesions
  - modified to include hypothermia, double ligation of the gubernaculum before its division and irrigation with distilled water

### What are the indications for vasoepididymostomy?

- testicular biopsy reveals complete spermatogenesis + absence of sperm in vasal fluid w/ no vasal or ED obstruction
  - perform if vasal fluid thick toothpaste w/o sperm, scant and thin w/o sperm, or dry vas w/o sperm

### What are the advantages and disadvantages of the different ways to perform V-E?

- intussusception (end-to-end)
  - Advantages
    - 2-3 sutures placed
    - bloodless anast
  - Disadvantages
    - cannot examine epididymal fluid prior to anast setup
- end-to-side
  - Advantages

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- bloodless anast
- minimally traumatic to epididymis
- can examine epididymal fluid prior to anast
- Disadvantages
  - difficult suture placement in collapsed tubule
- end-to-end
  - Advantages
    - can examine epididymal fluid prior to anast
    - easy and rapid identification of level of obstruction in epididymis
      - ◆ see gush of fluid → anast to this tubule
    - allows upward mobilization of epididymis to bridge large vasal gap
  - Disadvantages
    - difficult hemostasis on transected epididymis
      - ◆ harder to get blood-free sperm for cryo
    - difficult to identify proper tubule for anast
    - difficult outer layer closure
      - ◆ diameter of transversely transected epididymis is larger than outer diameter of vas → difficult to get watertight
    - sacrifices vasal blood supply from inferior epididymal artery

### Describe the technique of V-E.

- Preparation
  - testis delivered through high vertical 3-4cm scrotal incision
  - vas identified, isolated w/ Babcock, surrounded w/ Penrose
  - longitudinally incise vasal sheath, strip small segment of vas
  - vas hemitransected, sample vasal fluid
    - no sperm = epididymal obstruction → perform V-E
  - confirm vasal patency w/ NS vasogram
  - vas completely transected
  - open tunica vaginalis
  - select anastomotic site
    - should be proximal to site of suspected obstruction, proximal to visible granulomas
    - start as distal as possible
  - open tunica vaginalis w/ jeweler's scissors
    - oval opening should match outer diameter of vas
  - dissect epididymal tubules w/ sharp and blunt dissection
    - expose dilated loops of epididymis
  - needle from 10-0 nylon used to puncture tubule
  - sample epididymal fluid
    - close opening in tubule, move proximally until sperm found
  - vas secured near site w/ 2-4 sutures of 6-0 Prolene
  - posterior edge of epididymal tunic secured to vas w/ 9-0 nylon
- End-to-side
  - open selected tubule, sample fluid
  - aspirate sperm for cryo
  - indigo carmine used to stain cut tubule to outline mucosa
  - approximate posterior mucosal edge w/ 2 10-0 nylons
  - irrigate lumen w/ RL
  - anterior mucosal anast performed w/ 2-4 additional 10-0 nylons
  - outer muscularis and adventitia approximated to cut edge of epididymal tunic
  - secure vasal sheath to epididymal tunic
  - replace testis, close tunica vaginalis 5-0 Vicryl
  - close scrotum
- End-to-side intussusception
  - 3 double-armed 10-0 nylons placed in opened tubule in triangular fashion
  - open tubule after all 3 needles placed, sample fluid
  - each placed in lumen of vas, tied down
  - 2-stitch variation may be used
- End-to-end

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- epididymis dissected completely to vasoepididymal junction, transversely transected until gush of fluid seen exuding from cut surface
- single tubule w/ effluxing fluid selected, anastomosed directly to vas w/ 3-5 interrupted 10-0 nytons
- Post-op
  - bank sperm ASAP post-op when sperm appear

### What can one do during V-E if vasal length is severely compromised?

- dissect epididymis down to vasoepididymal junction, dissect off testis and flipped up to gain additional length
  - avoid injury to epididymal blood supply by staying right on tunica of testis
  - ligate inferior and middle epididymal branches of testicular artery if needed
- dissect convoluted vas to vasoepididymal junction

### What are the results after V-E?

- intussusception end-to-side: +ve SA in 50-85% patency
  - 65% at 1mo, 85% at 1yr
- end-to-side or end-to-end: 70% patency, 43% pregnancy rates

### What are the findings in ED obstruction?

- Px
  - at least 1 palpable vas
  - DRE: midline cystic structure
- SA
  - azoospermia or severe oligospermia or asthenospermia
  - low volume, acid semen pH, negative fructose
- Labs: normal FSH
- Testis biopsy: normal spermatogenesis
- TRUS
  - midline cystic lesion or dilated ED and SV

### What is the management of ED obstruction?

- TRUS guided aspiration of cystic structure or dilated ED
  - if motile sperm found, send for cryo
  - if no sperm found, perform vasography → if no sperm in either vas, perform MESA + cryo
    - **simultaneous TURED + V-E never works**
- inject 2-3cc indigo carmine + radioopaque dye
  - if resectable lesion, perform TURED

### Describe the procedure of TURED.

- TRUS w/ aspiration immediately prior to procedure
- bowel prep and antibiotics
- resectoscope w/ 24F loop engaged w/ finger in rectum
- resect verumontanum to reveal dilated ED orifice or cyst cavity
- preserve BN proximally and rectal mucosa posteriorly
- use pure cut until efflux of indigo carmine seen

### What are the complications of TURED?

- reflux
  - reflux of urine into ED → contaminates semen w/ urine
- epididymitis
  - may need chronic low-dose antibiotics
- retrograde ejaculation
  - use sudafed
- bleed, infection

### What are the results after TURED?

- increased semen volume in 2/3, sperm in SA in 50%

### What are the indications for electroejaculation?

- neurologic impairment
  - SCI, MS, DM, after RPLND

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- must have failed penile vibratory stimulation

### What are the complications of EEJ?

- autonomic dysreflexia
  - due to unopposed sympathetic discharge in men w/ complete SCI above T6
  - pre-treat w/ 20mg SL nifedipine
  - if occurs, stop procedure to break response

### How does one perform EEJ?

- pt in lateral decubitus
- empty bladder: 12-14F Foley + mineral oil
- inject 10cc buffer into bladder
- DRE, anoscopy performed: r/o rectal pathology
- rectal probe inserted, electrodes facing anteriorly
- stimulation started at 3-5V, increased in 1V increments w/ each stimulation
- record # stimulations to erection, ejaculation
- collect ejaculate
- if probe temp > 40°C, stop until < 38°C
- bladder recatheterized to collect any more sperm

### What are the various surgical techniques for sperm retrieval?

- MESA (microsurgical epididymal sperm aspiration)
  - technique similar to V-E
  - gentle compression enhances flow from incised tubule
  - sperm motility better more proximally in obstructed systems
  - pregnancy rates 60%
- PESA (percutaneous epididymal sperm aspiration)
  - if PESA fails, MESA will often fail as well → go directly to TESE/TESA
  - less reliable than MESA
  - cannot aspirate prior to entering epididymis: will get hydrocele fluid (bad for sperm)
- TESE (testicular sperm extraction)
  - microsurgical open technique: incise tunica, look for plumper seminiferous tubules and excise
    - sperm seen in 50%, w/ 50% pregnancy rate in these men
    - 19% spontaneous abortion rate: increased incidence of chromosomal abnormalities and DNA damage in men w/ nonobstructive azoospermia
  - percutaneous core biopsy
  - TESA (testicular sperm aspiration)

### What are the advantages and disadvantages of each surgical technique for sperm retrieval?

- MESA
  - Advantages
    - lower complication rate
    - epididymal sperm has better motility than testicular sperm
    - large # of sperm retrieved for cryo
  - Disadvantages
    - anaesthesia required
    - microsurgical skills required
    - not indicated for nonobstructive azoospermia
- PESA
  - Advantages
    - no microsurgical skill required
    - local anaesthesia only
    - epididymal sperm has better motility than testicular sperm
  - Disadvantages
    - hematoma, pain, vascular injury to testis/epididymis possible
    - variable success in finding sperm
    - smaller amount of sperm than MESA
    - not indicated for nonobstructive azoospermia
- TESA
  - Advantages

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- no microsurgical skill required
- local anaesthesia only
- can be used for nonobstructive azoospermia
- Disadvantages
  - immature/immotile testicular sperm
  - small quantity of sperm
  - poor results in nonobstructive azoospermia
  - hematoma, pain, vascular injury to testis/epididymis possible
- TESE
  - Advantages
    - low complication rate if microsurgical
    - preferred technique for nonobstructive azoospermia
  - Disadvantages
    - requires anaesthesia, microsurgical skills

### What are the indications for TESE?

- failure to find sperm in epididymis
- nonobstructive azoospermia

### What are the indications for IVF/ICSI?

- surgically unreconstructable obstruction (ex: CBAVD)
- few viable sperm in ejaculate
- azoospermic men w/ varicoceles
  - 50% of these men have enough sperm in ejaculate after varicocele repair
- men w/ nonobstructive azoospermia

### What is the incidence of varicocele?

- 15% of general population
- 35% of men w/ primary infertility
- 81% of men w/ secondary infertility

### How can one classify varicocele?

- Grade I: impulse felt in scrotum during Valsalva
- Grade II: veins palpated w/o Valsalva
- Grade III: veins visible

### What are the different ways of performing varicocele repair?

- Scrotal operations
  - do not perform: veins intertwined w/ arteries in scrotum, causes arterial injury + testicular atrophy
- Retroperitoneal repair
  - incise at the level of internal ring
  - split external and internal oblique
  - expose internal spermatic artery and veins retroperitoneally near ureter
- Laparoscopic repair
  - in essence, is retroperitoneal w/ same advantages and disadvantages
- Conventional inguinal
- Microsurgical inguinal and subinguinal repair
  - preferred approach
- Radiographic occlusion
  - balloon or coil occlusion of internal spermatic veins: successful in 75-90%

### What are the advantages and disadvantages of each form of varicocele repair?

- Retroperitoneal
  - Advantages
    - isolates veins proximally, near point of drainage into renal vein → only 1-2 veins present at this point
    - testicular artery not yet branched: often distinctly separate from veins
    - ?less potential for serious morbidity
  - Disadvantages
    - high incidence of recurrence: 15-25% → due to preservation of periarterial plexus of fine veins
      - ◆ may also be due to parallel inguinal or retroperitoneal collaterals



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- ◆ dilated cremasteric veins cannot be seen: also causes recurrence
- ◆ higher incidence of recurrence in kids (15-45%)
  - difficult to identify artery
  - working in deep hole, as vessels cannot be delivered into wound
  - difficult to identify lymphatics at this point, high incidence of hydrocele: 7-33%
- Laparoscopic varicocele repair
  - Advantages
    - improved visibility of artery, vas, lymphatics due to magnification: easily preserved
  - Disadvantages
    - high incidence of recurrence similar to retroperitoneal: 5-15%
    - more serious complications: injury to bowel, major vessels, air embolus
    - requires GA
    - much longer time to perform
    - hydrocele in 12%
- Microsurgical subinguinal/inguinal repair
  - Advantages
    - allow spermatic cord structures to be pulled up and out of wound: allows easy identification
    - allows access to external spermatic and gubernacular veins: prevents recurrence
      - ◆ recurrence rate low: 1%
    - little chance for serious morbidity
    - artery preserved
    - allows access to testis for biopsy
    - substantial decrease in hydrocele formation: 0-1%
  - Disadvantages
    - more veins encountered in subinguinal approach, artery surrounded
    - 2-3 branches of artery must be preserved
- Conventional inguinal
  - Advantages
  - Disadvantages
    - postop hydrocele formation 3-15%
- Radiographic occlusion techniques
  - Advantages
    - artery preserved
    - no hydrocele
  - Disadvantages
    - high incidence of recurrence: 15-25%
    - potential for serious morbidity: retrograde migration of coil into renal vein, femoral vein thrombosis/perf
    - long time for procedure: 1-3h

### Describe the technique of microsurgical inguinal/subinguinal varicocele repair.

- Anaesthesia: regional or light GA
- Inguinal/subinguinal approach
  - subinguinal: just below external ring
  - location of external ring determined
  - 2-3cm (or 3-4cm for inguinal) incision made
  - retract or divide superficial inferior epigastric vessels
  - inguinal: open external oblique
  - grasp spermatic cord w/ Babcock, deliver through wound, surround w/ Penrose drain
    - identify and exclude ilioinguinal and genitofemoral
- Delivery of the testis
  - deliver testis through incision, divide all scrotal and gubernacular collaterals
  - identify and ligate all external spermatic veins
  - return testis into scrotus
- Dissection of the cord
  - use operating microscope
  - open internal and external spermatic fasciae
  - identify cord for pulsations, revealing the location of the testicular artery
  - dissect out artery, encircle w/ vessel loop
    - identify by lifting vessel w/ microforceps: loop for pulsating blush of blood
    - often found adherent to underside of large vein

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- strip veins clean, all doubly ligated w/ clips or 4-0 silk
- preserve vasal veins for venous return
  - only divide if > 3mm in diameter
  - only need one set of vasal veins
- return cord to its bed
- Closure
  - external oblique reapproximated if opened
  - close Scarpa's w/ 3-0 Monocryl
  - close Camper's w/ 4-0 absorbable
  - close skin w/ subQ
- Postop
  - scrotal support
  - back to work in 2-3d (2.8d on average in US studies)

### What are the complications of varicocele repair?

- hydrocele
  - most common complication
  - due to lymphatic obstruction
- testicular artery injury
  - may cause testicular atrophy +/- impaired spermatogenesis
  - 14% chance of injury when testicular artery purposefully ligated
- recurrence
  - more common after nonmicrosurgical repair
  - retroperitoneal procedures miss inguinal collaterals

### What are the results after varicocele repair?

- improved SA in 60-80%
  - return of sperm to SA in 50% of azoospermic men w/ palpable varicoceles
  - repair of larger or bilateral varicoceles results in more improvement in SA
- pregnancy in 20-60%
  - 43% pregnant by 1yr
- improved T if low

### What are the different ways of performing hydrocele repair?

- Excisional techniques
  - most certain to result in elimination of hydrocele
  - Indications: long-standing hydroceles w/ thick-walled sacs, multiloculated hydroceles
  - edges oversewn w/ 4-0 chromic
  - Jaboulay procedure: sac edges oversewn behind the cord → leave 1cm to prevent constriction of the cord
- Plication techniques (Lord)
  - Indications: thin hydrocele sac
  - Contraindication: multiloculated hydrocele, long-standing thick hydrocele sac
  - sac is not dissected: sac opened and cut edges cauterized and oversewn
  - 8-12 sutures to plicate sac
- Window operations
  - quick and bloodless, but high recurrence rates
  - most suitable for small hydroceles
  - 1-2cm buttonhole removed in sac in avascular area
  - edges oversewn
- Dartos pouch technique
  - suitable for thin-walled sacs
  - no sac dissection, minimal bleeding
  - testis delivered, cut edges of sac opening oversewn or cauterized
  - dartos pouch created like orchidopexy
- Sclerotherapy
  - tetracycline or other irritating agents
  - may cause epididymal obstruction
  - use in older pts w/ no need for fertility

### What are the complications of hydrocele repair?

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- hematoma: most common
- injury to epididymis or vas

### What is the definition of chronic orchialgia?

- intermittent or constant scrotal pain, either unilateral, bilateral, or alternating, lasting > 3mo

### What are the causes of chronic orchialgia?

- chronic epididymitis
  - persistently tender indurated epididymis
  - +ve urine cultures, treat w/ antibiotics depending on C&S
  - may need epididymectomy if fertility not an issue
- varicocele
  - persistent aching discomfort, relieved when pts in supine position
- post-hernia repair orchialgia
  - due to nerve entrapment: usually to resolves w/ conservative management
  - if not resolving, operate to remove any nonabsorbable suture material
- chronic intermittent torsion
  - episodes of sudden onset of testicular pain, associated w/ N/V, testis elevated and transverse-lying
  - spontaneously disappears after few min-hrs
  - bilateral orchidopexy
- postvasectomy pain syndromes
  - present in 30%, difficult to treat
  - chronic congestive epididymitis
    - due to continued production of sperm and fluid, distending epididymis
    - chronic, dull, aching pain, worsened by ejaculation
    - tx: NSAIDs, sitz baths x 3mo
      - ◆ if no relief, try spermatic cord blocks or local intralesional steroids
      - ◆ last resort: vasectomy reversal or epididymectomy → 90% chance relieving pain w/ reversal
  - sperm granuloma
    - due to leakage of sperm from testicular end of vas
    - tx: removal of granuloma w/ intraluminal cautery
- chronic orchialgia of unknown etiology
  - DDx: LUTS, distal ureteral stones, hernia, IBS, referred pain
  - tx: NSAIDs, sitz baths, scrotal support x 3mo
    - microsurgical total denervation of spermatic cord: success in 80%
      - ◆ mobilize testis and cord like varicocele, preserving vas, vessels, testicular artery, and 1-2 lymphatics while transecting the rest of the cord





## Chapter 45

### • Physiology of Penile Erection and Pathophysiology of ED and Priapism •

#### What are the functions of the following penile components during erection:

- corpora cavernosa: supports sponge and glans
- tunica albuginea (of cavernosa): contains and protects erectile tissue, provides rigidity, contributes to veno-occlusive mechanism
- smooth muscle: regulates blood flow in and out of sinusoids
- ischiocavernosus muscle: pumps blood distally to speed up erection, provides additional rigidity during rigid erection state
- bulbocavernosus muscle: compresses bulb to expel semen during ejaculation
- corpus spongiosum: provides pressurized narrow chamber to expel semen
- glans: cushion to lessen impact, sensory input to facilitate erection, cone shape facilitates intromission

#### Describe the structure of the tunica albuginea.

- cavernosa: bilayered structure
  - composed of elastic fibers making irregular latticed network
  - inner layer of circular bundles: support and contain cavernous tissue
    - intracavernosal pillars radiate inwards, acting as struts
  - outer longitudinal layer: insert into inferior pubic rami
    - absent b/w 5 and 7 o'clock
  - emissary veins run b/w inner and outer layers in oblique manner
- spongiosum
  - one layer of circular only: no outer longitudinal layer
  - no intracorporeal struts → low pressure

#### What prevents occlusion of the cavernous arteries during erection?

- path of artery: more direct route than emissary veins
- protected by periarterial soft tissue sheath

#### Where is the most vulnerable area of the tunica in terms of strength and thickness?

- ventral groove (5-7 o'clock)
  - lacks the longitudinally directed outer-layer bundles

#### Describe the vascular supply to the penis.

- Arterial
  - Skin: superficial external pudendal
    - arise from first portion of femoral artery, divide into 2 main branches
  - Deep structures: internal pudendal → common penile artery → 3 branches:
    - bulbourethral artery: enters sponge
    - dorsal artery: ends in glans
    - cavernosal artery: gives off helicine arteries
  - internal pudendal (from internal iliac) → common penile + perineal artery (supplies scrotal skin via posterior scrotal artery)
  - accessory arteries: external iliac, obturator, vesical, femoral
- Venous – 3 systems:
  - superficial dorsal vein (from skin) → L saphenous vein
  - sinusoids → subtunical venular plexus → emissary veins from corpora and sponge → laterally to circumflex veins, dorsally to deep dorsal veins (w/i Buck's) + periurethral veins → Santorini's plexus
  - crural veins + cavernosal veins → internal pudendal veins → internal iliac vein (through Alcock's canal)
- Lymphatics
  - glans → large trunks in frenulum → traverse beneath Bucks → terminate in deep inguinal LN of femoral triangle

## Chapter 45 Questions - Erections.doc

### Describe the events that occur during erection in the corpora cavernosa.

- dilation of arterioles by increased blood flow
- trapping of blood in sinusoids
- compression of subtunical venular plexuses, decreasing venous outflow
- stretching of tunica to capacity, enclosing the emissary veins b/w the inner circular and outer longitudinal layers
- increase in intracavernosal pressure to 100 mmHg, raising penis to erect state (full erection)
- increase in intracavernosal pressure to several hundred mmHg during contraction of the ischiocavernosus (rigid erection)

### What are the determinants of the angle of the erect penis?

- penile size
- attachment to the puboischial rami (crura) and anterior pubis (suspensory and fusiform ligaments)

### What are the different phases of detumescence?

- 1st: transient increase in intracorporeal pressure: indicates beginning of sm. muscle contraction against a closed venous system
- 2nd: slow pressure decrease, from slow reopening of venous channels w/ resumption of baseline arterial flow
- 3rd: fast pressure decrease, w/ fully restored venous outflow

### What neural pathways are present that control erection?

- Peripheral
  - Autonomic
    - Sympathetics
      - ◆ sympathetics originate from T10/11-L2
        - ◆ pass through white rami → sympathetic chain ganglia
      - ◆ T10-T12 fibers pass thru thoracolumbar splanchnic nerves to aorticorenal ganglion and inferior mesenteric ganglion
        - ◆ pass to superior hypogastric plexus, hypogastric nerves, then inferior hypogastric (pelvic) plexus, join w/ parasympathetics
        - ◆ go to vesical plexus, then cavernous nerves
      - ◆ responsible for detumescence
    - Parasympathetics
      - ◆ preganglionic fibers arise from neurons in intermediolateral cell columns of S2-4, pass through pelvic splanchnic nerves (nervi erigentes) to pelvic plexus (inferior hypogastric plexus) → vesical plexus → cavernous nerves
        - ◆ joined by sympathetic nerves to form ?superior hypogastric plexus
      - ◆ stimulation of parasympathetics causes erection
  - Somatic
    - thin myelinated A<sub>δ</sub> and unmyelinated C fibers originating in skin, converge to form dorsal nerve of penis
    - becomes pudendal nerve, runs through Alcock's canal, and enters cord at S2-4
      - ◆ terminates in central gray region of lumbosacral segment
    - responsible for sensation and contraction of bulbocavernosus and ischiocavernosus
- Supraspinal
  - medial preoptic area and paraventricular nucleus of hypothalamus and hippocampus integrate sexual function and erection
  - cerebral impulses travel through sympathetics (?inhibitory interneurons to inhibit NE release), parasympathetic (to release NO and ACh), and somatic (to release ACh) to produce erection

### What spinal reflexes are involved in stimulation of the dorsal nerve of the penis?

- bulbocavernosus reflex: noxious abrupt stimulation of sacral motor neurons, travels along pudendal nerve (motor) to cause BCR
- BN closure reflex: low intensity continuous stimulation travels to sacral parasympathetic neurons and interneurons, then pelvic and cavernous nerves, inhibiting bladder and closing BN
- erection and ejaculation: high-intensity continuous stimulation, travelling to sacral motor and parasympathetic and thoracolumbar sympathetic neurons, then to pudendal/pelvic/cavernous nerves, causing erection/ejaculation

### What brain centers are involved in sexual function?

- Forebrain
  - medial amygdala: control sexual motivation
  - stria terminalis
  - pyriform cortex: inhibits sexual drive (hypersexuality when destroyed)

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- hippocampus: involved in penile erection
- R insula and inferior frontal cortex: increased activity during visually evoked sexual stimulation (sexual arousal)
- L anterior cingulate cortex
- Hypothalamus
  - medial preoptic area (MPOA): enables ability to recognize sexual partner, integration of hormonal and sensory cues
  - paraventricular nucleus (PVN): facilitates erection via oxytocin neurons to lumbosacral spinal autonomic and somatic efferents
- Brain stem
  - nucleus paragigantocellularis: inhibits erection via serotonin neurons to lumbosacral spinal neurons and interneurons
  - A5 catecholamine cell group, locus coeruleus: NE innervation of anterior horn motoneurons to perineal striated muscles
- Midbrain
  - periaqueductal gray matter: relay center for sexually relevant stimuli

What is the center of somatomotor penile innervation in the spine?

- Onuf's nucleus (S2-4)

### What are the 3 types of erection?

- psychogenic
  - from AV stimuli or fantasy: stimulation of T11-L2 and S2-4 causes erection
- reflexogenic
  - from tactile stimuli to genital organs: impulses reach spinal erection centers
  - preserved in upper SCI
- nocturnal
  - occurs during REM sleep: cholinergic neurons in lateral pontine tegmentum

### What neurotransmitters are involved in erection and detumescence?

- Peripheral
  - Flaccidity and detumescence
    - **NE: primary NT to control flaccidity**
    - endothelin: potent vasoconstrictor
    - TXA<sub>2</sub>, PGF<sub>2α</sub>, LTs, ANGII
  - Erection
    - ACh: contributes indirectly by presynaptic inhibition of sympathetics + stimulation of NO release
      - ◆ release of NE inhibited by PGE<sub>1</sub>
    - **NO, cGMP: NO released from NANC terminals is the principal NT involved in erection**
      - ◆ NO increases cGMP production, which relaxes cavernous smooth muscle
    - VIP: VIP-induced smooth muscle relaxation prevented by NOS inhibitors
      - ◆ VIP may stimulate NO production
- Central
  - Flaccidity and detumescence
    - Serotonin
      - ◆ cell bodies in midline raphe nuclei of brain stem, project to portion of hypothalamus
      - ◆ 7 different R: 5HT-1 (A,B,D,E,F subtypes), 5HT-2 (A,B,C subtypes)
      - ◆ 5HT pathways inhibit copulation
      - ◆ 5HT-1A inhibit erection but facilitate ejaculation, 5HT-2 agonists stimulate erection but facilitate seminal emission and ejaculation, 5HT-2C stimulation causes erection
    - Opioids: may have inhibitor control over oxytocinergic transmission
    - Prolactin: increased PRL suppresses sexual function
      - ◆ may inhibit dopaminergic action in MPOA and decreased T level
      - ◆ may have direct contractile effect on smooth muscle in penis
  - Erection
    - Dopamine
      - ◆ cell bodies in ventral tegmentum, substantia nigra, and hypothalamus
      - ◆ dopaminergic neurons activate oxytocinergic neurons in the PVN, and release of oxytocin produces erection
      - ◆ 5 different R: apomorphine stimulates D<sub>1</sub> and D<sub>2</sub> receptors, inducing penile erection
      - ◆ dopamine agonists: apomorphine and pergolide
      - ◆ dopamine uptake inhibitors: nomifensine and bupropion
    - NE

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- ◆ cell bodies in locus coeruleus and A5 catecholamine cell group in pons and medulla, project to PVN, supraoptic, and hypothalamus, thalamus, neocortex
- ◆ inhibition of NE release by clonidine ( $\alpha_2$ -agonist): decrease in sexual behaviour
- ◆ yohimbine ( $\alpha_2$ -antagonist): increases sexual activity
- Oxytocin
  - ◆ secreted by posterior pituitary and PVN
  - ◆ increased during sexual activity, produces yawning and erection

### What is the principal NT thought to control flaccidity?

- NE

### What is the principal NT thought to control erection?

- NO

### What are the different forms of NOS?

- neuronal NOS (NOS-1, nNOS)
- inducible NOS (NOS-2, iNOS)
- endothelial NOS (NOS-3, eNOS)

### Describe the molecular mechanism of smooth muscle relaxation in the penis.

- NO created in endothelial cells by eNOS from L-arginine +  $O_2 \rightarrow NO + L$ -citrulline
- NO released from nerve endings (NANC terminals) or endothelial cells
  - activates soluble guanylyl cyclase, producing cGMP (2<sup>nd</sup> messenger)
  - may also stimulate opening of Na-K-ATPase channels, causing hyperpolarization and preventing contraction
- cGMP activates cGMP-specific protein kinase
  - phosphorylates and inactivates myosin light-chain kinase
    - causes dissociation of myosin and actin and smooth muscle relaxation
  - also activates K channels, causing hyperpolarization and decrease in intracellular Ca
- cGMP hydrolyzed to GMP by phosphodiesterases PDE type 5 (PDE-5)
  - PDE 5, 6, and 11 are specific for cGMP as substrate
  - PDE 2, 3, 4 found in cavernosum, but do not play role in erection

### Describe the molecular mechanism of smooth muscle contraction in the penis.

- NE from sympathetic nerve endings (1<sup>st</sup> messenger) + endothelins from endothelial cells stimulate a G protein
  - G protein activates PLC, which hydrolyses  $PIP_2 \rightarrow DAG$  and  $IP_3$
  - DAG: causes PKC stimulation, which opens Ca channels, increasing intracellular Ca concentration
  - $IP_3$ : stimulates release of intracellular Ca from ER
- increased intracellular Ca binds to calmodulin, changing configuration to expose sites of interaction w/ myosin light-chain kinase
  - Ca-calmodulin complex binds to myosin light-chain kinase, activating it
  - active Ca-calmodulin-MLCK complex phosphorylates myosin light chains
- phosphorylation of light chains allows cycling of myosin cross-bridges along actin → smooth-muscle contraction
  - also activates myosin ATPase, which hydrolyzes ATP to provide energy for contraction

### What are the 4 major types of ion channels?

- external ligand-gated: open to specific extracellular molecule (ex: ACh)
- internal ligand-gated: open or close to specific intracellular molecule (ex: ATP)
- voltage gated: open in response to change in membrane potential (ex: Na, K, Ca channels)
- mechanically gated (open in response to mechanical pressure)

### What channels regulate entry and exit of Ca from cells?

- Ca channels: major inflow regulators
- Ca-Na exchangers: regulate Ca exit
- Ca-ATPase: regulate Ca exit

### What K channels have been found to exist in cavernous smooth muscle?

- Calcium sensitive K channel (maxi-K channel) → may be involved in cAMP-mediated smooth muscle relaxation
- metabolically regulated K channels ( $K_{ATP}$ )
- delayed rectifier
- fast transient A current ( $I_A$ )



## Chapter 45 Questions - Erections.doc

### What other tissues express PDE5 other than corpus cavernosum?

- platelet, lung, cerebellum, spinal cord, skeletal muscle, heart, placenta, pancreas, intestine, aorta, adrenal

### Why do pts have visual disturbances w/ PDE5 inhibitors?

- crossover w/ PDE6 in the retina

### What is the incidence of erectile dysfunction?

- 35% of married men > 60
- MMAS study, from 40-70 yrs
  - complete ED: 5% increasing to 15%
  - moderate ED: 17% → 34%
  - mild ED: steady at 17%

### How can one classify the various types of erectile dysfunction?

- Etiology
  - Organic
    - Vasculogenic
      - ◆ Arterial
        - ♦ atherosclerosis or trauma may decrease perfusion pressure and flow to sinusoidal spaces
        - ♦ RF: htn, increased chol, smoking, DM, trauma, pelvic rads, long-distance cycling
      - ◆ Cavernosal (venogenic)
        - ♦ large venous channels draining corpora
        - ♦ degenerative changes (Peyronie's, DM, age) or trauma (fracture) resulting in inadequate compression of emissary veins
        - ♦ structural alterations in fibroelastic components of trabeculae, smooth muscle (or its ion channels), and endothelium causing leak
        - ♦ insufficient smooth muscle relaxation: anxiety
        - ♦ operative correction of priapism: shunts
      - ◆ Mixed
    - Neurogenic
      - ◆ brain
        - ♦ Parkinson's, stroke, encephalitis, temporal lobe epilepsy, tumours, dementia, Alzheimer's, Shy-Drager, trauma
      - ◆ cord lesions
        - ♦ SCI: degree of ED depends on location and extent of lesion
          - reflexogenic erection preserved in 95% of pts w/ complete UMN lesions, 25% of complete LMN lesions
          - thoracolumbar pathway may compensate in sacral lesions
        - ♦ spina bifida, disc herniation, syringomyelia (cyst in cord), tumour, transverse myelitis, MS
      - ◆ peripheral nerves
        - ♦ surgery, trauma
        - ♦ pelvic #: may be due to cavernous nerve injury or vascular injury
        - ♦ alcoholism, vitamin deficiency, DM: may affect peripheral nerves
        - ♦ decreased penile tactile sensitivity w/ increasing age
    - Anatomic
    - Endocrinologic
      - ◆ hypogonadism
        - ♦ T increases sexual interest, increases frequency of sexual acts, and increases freq of nocturnal erections
        - ♦ castration decreases arterial flow, induces venous leakage, and decreases erectile response
      - ◆ hyperprolactinemia
        - ♦ due to pituitary adenoma or medications: causes reproductive and sexual dysfunction
        - ♦ sx: loss of libido, ED, galactorrhea, gynecomastia, and infertility
        - ♦ increased PRL associated w/ decreased T due to inhibition of GnRH by elevated PRL
      - ◆ hyperthyroidism: decreased libido due to increased estrogens
      - ◆ hypothyroidism: low T and elevated PRL cause ED
      - ◆ DM: causes ED through vascular, neurologic, endothelial, and psychogenic complications
    - Drug induced
    - Aging, systemic disease, or other causes
      - ◆ DM: ED in 35-75%, high prevalence of arterial insufficiency

## Chapter 45 Questions - Erections.doc

- ◆ hyperlipidemia and atherosclerosis: decreased NOS activity, increased contractile TX and PG
- ◆ htn: associated stenotic lesions cause ED
- ◆ CRF: impaired libido, ED, infertility → multifactorial: decreased T, increased PRL, DM, vascular insufficiency, meds, neuropathy, stress
  - ◆ improved after transplantation
- ◆ pulmonary disease, MI: fear aggravation of sx
- ◆ cirrhosis, scleroderma, chronic debilitation, cachexia
- Psychogenic: either direct inhibition of the spinal erection center by the brain due to exaggerated normal suprasacral inhibition, or excessive sympathetic outflow, which increases penile smooth muscle tone
  - Generalized type
    - ◆ Generalized unresponsiveness: primary lack of arousability, age-related decline in arousability
    - ◆ Generalized inhibition: chronic disorder of sexual arousability
  - Situational type
    - ◆ Partner related: lack of arousal in specific relationship, lack of arousal due to sexual object preference, or high central inhibition due to partner conflict or threat
    - ◆ Performance related: associated w/ other sexual dysfunction (ex: rapid ejaculation), situational performance anxiety (ex: fear of failure)
    - ◆ Psychologic distress or adjustment related: associated w/ negative mood state (depression) or major life stress (death of partner)
- Neurovascular
  - failure to initiate: neurogenic
  - failure to fill: arterial
  - failure to store: venous

### What drugs can cause ED?

- antipsychotics: disturb central NT pathways
- tranquilizers: sedation, anticholinergic actions, central antidopaminergic effect,  $\alpha$ -antagonist action, release PRL
- antidepressants: all 4 types (TCA, heterocyclic, SSRI, MAOI) cause ED except for bupropion (Wellbutrin) and trazodone
  - incidence of ED: fluoxetine (1.7%), sertraline (2.5%), paroxetine (6.4%)
  - various peripheral and central effect
- antihypertensives
- central sympatholytics: methyl dopa, clonidine (inhibition of hypothalamic center by  $\alpha_2$ -agonist) and reserpine (MAO inhibition causing depletion of catechol stores and 5-HT)
- $\alpha$ -blockers: phenoxybenzamine, phentolamine → retrograde ejaculation or ejac failure
- $\beta$ -blockers: central side effects (sedation, sleep disturbances, depression), reduced antagonism of  $\alpha$  vasocontractile forces
- diuretics: thiazides, spironolactone → associated w/ ED, gynecomastia, mastodynia
  - spironolactone interferes w/ T synthesis
- smoking: causes vasoconstriction and leakage
- EtOH: improved erection in small amounts
  - large amounts cause sedation, decreased libido, and ED
  - chronic: liver dysfunction, decreased T, increased estrogen, alcoholic polyneuropathy
- cimetidine ( $H_2$  receptor antagonist): suppression of libido and ED → antiandrogen and increases PRL
- estrogens
- antiandrogens: ketoconazole, cyproterone acetate
- anticancer drugs: loss of libido, peripheral neuropathy, azoospermia, ED

### What changes in erection have been seen in men as they age?

- greater latency to erection
- less turgid erection
- loss of forceful ejaculation
- decreased ejaculatory volume
- longer refractory period
- decrease in penile tactile sensitivity

### What are the proposed mechanisms of ED in men w/ DM?

- impaired NO synthesis
- increased endothelin B receptor binding sites and ultrastructural changes
- increased oxygen free radicals and oxidative stress injury
- NO-dependent selective nitrergic nerve degeneration

## Chapter 45 Questions - Erections.doc

- increased levels of glycosylated end products

### How can one classify priapism?

- Ischemic (veno-occlusive)
  - more common: painful, rigid erection characterized by absent cavernous blood flow
  - beyond 4hrs: emergency
- Non-ischemic (arterial)
  - less common: due to unregulated cavernous inflow
  - usually not fully rigid, painless
  - corpora continue to be filled w/ well-oxygenated blood

### What are the causes of priapism?

- Idiopathic (Primary)
- Secondary:
  - Thrombo-Embolic
    - sickle-cell: 6.4% incidence, due to sludging of blood in corpora, blocking subtunical venules → usually recurs
    - leukemia, fat emboli, thalassemia, prolonged sexual activity
  - Iatrogenic: intracavernous injection, AV or arteriocavernous bypass surgery
    - 5.3% incidence w/ ICI
  - Neurogenic: SCI, cauda equina, autonomic neuropathy, spinal stenosis, anesthesia
    - due to release of erection-inducing NTs from parasympathetics or interference w/ tonic inhibition from sympathetics
  - Neoplastic: prostate, lung, bladder, RCC
  - Traumatic: perineal or genital → usually high-flow
    - due to laceration of cavernous artery or branches within corpora cavernosae
  - Infectious or toxic: malaria, rabies, scorpion sting
  - Meds and chemicals
    - Antidepressants: bupropion, trazodone, fluoxetine, sertraline, Li
      - ◆ priapism due to  $\alpha$ -blocking actions or stimulation of 5HT-2C/1D receptors
    - Antipsychotics: clozapine
    - Tranquilizers: mesoridazine, perphenazine
    - Antianxiolytics: hydroxyzine
    - Psychotropics: CPZ
    - $\alpha$ -blockers: prazosin
    - hormones: GnRH
    - anticoagulants: heparin, warfarin
    - recreational drugs: cocaine, EtOH
    - TPN: use 10% fat emulsion infused slowly to prevent priapism, mixed w/ amino acid/dextrose solution

### How does TPN cause priapism?

- increase in blood coagulability
- adverse effect on cellular elements of blood
- fat emboli

### What is the natural hx of priapism?

- Ischemic
  - after several days, corporal tissue becomes thickened, edematous, and fibrotic
    - trabecular interstitial edema after 12h
      - ◆ destruction of sinusoidal endothelium, exposure of BM
    - thrombocyte adherence by 24h
    - 48h: thrombi noted in sinusoidal spaces, smooth muscle necrosis and fibroblast transformation
  - impaired contractile response w/ anoxia or metabolic acidosis, increase in intracellular Ca and relaxation
  - lack of thrombosis in penile blood: cavernous fibrinolytic activity 3X peripheral blood → local coagulopathy
  - natural sequelae: complete ED
- Non-ischemic
  - regain adequate erection after embolization or surgical ligation or ruptured artery
  - may take weeks-months



## **Chapter 46**

### **• Evaluation and Nonsurgical Management of ED and Priapism •**

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**What are the indications for a complete ED evaluation? → mnemonic: CaNT use PP? PooR ME**

- Cardiac: high-risk cardiac conditions
- Neurologic disease
- Trauma: pelvic/perineal trauma
- Primary ED present since puberty
- Peyronie's disease
- Psych: significant psychologic component to ED (depression, anxiety)
- Resistant: oral-agent resistant ED
- Medical: multiple medical problems
- Endocrinopathy: DM

**What is the "Process of Care Model for the Evaluation and Treatment of ED"?**

- stepwise linear model for treatment of ED
  - 1<sup>st</sup> line therapies: oral agents, vacuum erection devices, and couple/sexual therapy
  - 2<sup>nd</sup> line and 3<sup>rd</sup> line therapies: MUSE, ICI, surgical prosthetic
- referral based on failure of 1<sup>st</sup> line therapy
  - common indications: treatment failure, penile curvature, young pts, trauma, vascular/neurosurgical intervention required, complicated endocrinopathy, psychiatric d/o, pt request

**What is the definition of ED?**

- 1<sup>st</sup> International Consultation on ED (1999)
  - consistent or recurrent inability to maintain erection sufficient for sexual performance
  - 3month duration required
    - exception: trauma, surgically induced
  - ED should not be used to describe curvature, priapism, painful erection, rapid ejaculation, anorgasmia, or loss of libido

**What is involved in the diagnosis of ED in the new pt?**

- History
  - start all hx explaining that RF exist for ED, ask in non-threatening and permissive manner
    - htn, CAD, PVD, DM, smoking, medications
  - CC: performance, satisfaction, interest
  - social hx: marital status, problems w/ partner
  - sexual hx: sexual orientation, % satisfactory sexual encounters to pt/partner
    - libido, how much sex does pt want?
  - ED hx
    - onset, circumstances of ED, course, noncoital erection, nocturnal erection, morning erections
    - partner specific
    - last N erection, last sexual attempt
    - erectile stiffness (nocturnal/during sex), initiation w/ stimulation, maintain w/ stimulation
    - loss of erection prior to climax
    - need to concentrate
    - pain w/ erection
    - difficult sexual positions
    - previous therapy
  - medical hx
    - DM, CRF, smoking, EtOH, psychologic, neurologic, chronic disease, htn, CAD
    - pelvic surgery, rads, pelvic trauma
  - psychosocial hx: psychosexual problems, anxiety, fear
  - ED impact questionnaires

## Chapter 46 Questions - ED.doc

- Physical
  - BP if none in past 3-6mo → r/o htn
  - body habitus: genetic syndromes (Kallman's, Klinefelter's), virilization and body hair, signs of hypogonadism
  - CVS exam
  - neurologic exam: peripheral neuropathy, BCR → r/o neurogenic impotence
  - genital exam: micropenis, chordee, Peyronie's
  - testes: small, soft, atrophic
  - gynecomastia → search for hypogonadism or increased PRL
  - DRE
- Labs
  - recommended: HbA<sub>1c</sub>, lipid profile, fasting glucose, testosterone
  - optional: PRL, LH, TSH, CBC, U/A
  - PSA: before hormones started
- Consults
  - psychological consult: optional
- Specialized evaluation
  - NPTR
  - AV sexual stimulation and vibratory stimulation (AVSS/PTR)
    - used as a screening tool to r/o psychogenic ED
    - cannot distinguish among men w/ organic causes of ED
  - neurophysiologic testing: rarely changes management, no reliable test for NT release
    - Somatic
      - ◆ biothesiometry: measures sensory perception threshold to various vibratory stimulation → poor results
      - ◆ sacral evoked response – BCR latency
        - ◆ 2 electrodes placed in R and L bulbocavernosus muscles, 2 stimulating electrodes in penis (corona, midshaft)
        - ◆ latency period measured from beginning of stimulus to beginning of response
        - ◆ abnormal BCR latency is > 3SD above mean (30-40msec)
      - ◆ dorsal nerve conduction velocity: average conduction velocity 21-29m/sec in normal men
      - ◆ genitocerebral evoked potential studies: electrical stimulation of dorsal nerve (like BCR latency)
        - ◆ instead of measuring EMG response, measure evoked potential waveforms overlying sacral spinal cord and cerebral cortex
        - ◆ assesses presence, location, and nature of afferent penile sensory dysfunction
    - Autonomic
      - ◆ HR variability and sympathetic skin response (SSR)
        - ◆ measure HR variations during quiet breathing, deep breathing, and in response to raising one's feet
        - ◆ BP control measures BP response to standing: should have decrease < 13mmHg
        - ◆ SSR measures skin potential evoked by electrical shock stimuli: SSR present in all pts w/ non-neurogenic ED
      - ◆ corpus cavernosum EMG (CC-EMG) and single potential analysis of cavernous electrical activity
        - ◆ direct recording of cavernous electrical activity w/ needle electrode during flaccidity and w/ visual sexual stimulation
        - ◆ normal flaccid activity: rhythmic slow wave w/ intermittent burst of activity
        - ◆ bursts stop during sexual stimulation, returns during detumescence
        - ◆ CC-EMG characterized by highly reproducible waveforms (AP)
  - specialized endocrinologic testing: routine testing controversial → overall endocrinopathy in ED pts 17.5% (1.7-35%)
    - Johnson and Jarow criteria: libido decrease, atrophic testes → neither predict for hypogonadism
      - ◆ age < 50: hormone profile if J&J criteria met
      - ◆ age > 50: routine hormonal profile (T: free and total)
    - total T, free T, % free T
      - ◆ if total T abnormal in pts < 50 or free T abnormal in elderly/obese pt, get early morning T, serum LH
    - 3 early morning blood samples for T, 15-20min apart (early morning peak: 4am)
      - ◆ bioavailable T (free + albumin bound): most reliable assessment of gonadal function
    - PRL: can inhibit LH secretion
    - serum estradiol, AR on genital skin: in pts w/ gynecomastia or suspected androgen resistance (increased T/LH w/ undermasculinization)
    - adrenal fn: in pts w/ rapid loss of sexual characteristics
    - thyroid function
  - vascular diagnostics

## Chapter 46 Questions - ED.doc

- 1<sup>st</sup> line evaluation of penile blood flow: ICI and stimulation test
  - ◆ give ICI w/ 10-20µg of alprostadil through 27-29G needle into corpus cavernosum, visual rating of subsequent erection → most common test for ED
    - ◆ at this dose, only 4% of men have rigid erection > 2h → give phenylephrine
  - ◆ full erection usually achieved in 15min, lasts longer than 15min → self-stimulation if no response in 15min
  - ◆ abnormal test suggests penile vascular disease: may be due to anxiety, so give pts privacy
- 2<sup>nd</sup> line
  - ◆ penile blood flow study (PBFS) w/ duplex US (gray-scale) = ICI + measurement w/ Doppler US
    - ◆ most reliable and least invasive assessment of ED
    - ◆ can selectively target cavernosal vessels
  - ◆ color duplex Doppler US (CDDU): aids in visualizing vessels by assigning color to flowing blood
    - ◆ best tool to diagnose high-flow priapism
    - ◆ flaccid cavernous arterial flow measurements have no value
  - ◆ Doppler penile blood flow study
    - ◆ PSV: velocities measured 10-15 min after injection in dorsal and each cavernous artery
      - **PSV within cavernous artery should be > 25cm/sec** within 5min: if < 25cm/sec, predicts severe CAD
      - symmetry: asymmetry > 10cm/sec or reversal across collateral may mean atherosclerotic lesion
      - slow response in hypertensive/anxious pt, rapid response in neurogenic ED
    - ◆ **end-diastolic velocity (EDV): > 5-7 cm/sec** is normal
    - ◆ cavernosal arterial diameter, presence of communication b/w cavernous arteries or b/w dorsal and cavernous
    - ◆ increase in penile arterial velocity after ICI + increase in **arterial diameter → should increase by 75%**
      - normally 1-1.5mm during pharmacologic tumescence
    - ◆ systolic rise time: time from start of systolic velocity to max value
    - ◆ blood flow acceleration = PSV/systolic rise time (time from start of systolic velocity to max value)
    - ◆ anatomic variations: # and locations of arteries, branching, distal arterial perforators
  - ◆ Power Doppler
- 3<sup>rd</sup> line
  - ◆ cavernous arterial occlusion pressure
    - ◆ infuse NS into corpora to raise intracavernous pressure > sBP
    - ◆ stop infusion, allow intracavernous pressure to fall while applying Doppler to penile base
    - ◆ cavernous artery systolic occlusion pressure (CASOP) = pressure at which the cavernous arterial flow detected
    - ◆ normal = difference in cavernous and brachial pressure < 35mmHg
  - ◆ radioisotopic penography
    - ◆ use <sup>99m</sup>Tc-labelled RBC to quantify changes in penile blood volume after ICI
    - ◆ separates pts w/ extremely low flow from normal flow
  - ◆ MRI/MRA
    - ◆ restrict to pts w/ hx of pelvic trauma that are candidates for penile revascularization
  - ◆ arteriography
    - ◆ reserved for pts that are candidates for penile revascularization
    - ◆ perform ICI + selective cannulation of internal pudendal artery and injection of dilute contrast
    - ◆ study inferior epigastrics: used most commonly for revascularization
  - ◆ cavernosometry and cavernosography
    - ◆ cavernosometry: NS infusion (+/- alprostadil) + intracorporeal pressure monitoring
      - NS infusion rate necessary is directly related to degree of venous leakage
      - inability to increase intracorporeal pressure to sBP (or rapid drop after stop) = veno-occlusive dysfunction
      - **MFR (maintenance flow rate): normal < 3-5cc/min**
        - flow required to maintain erection at intracavernous pressure of 150mmHg
    - ◆ cavernosography: infusion of contrast into corpora during artificial erection to visualize site of leakage
      - venous ligation procedures → poor results
  - ◆ cavernous biopsy: controversial
    - ◆ smooth muscle: less smooth muscle/more collagen in elderly w/ veno-occlusive dysfunction
    - ◆ ECM
    - ◆ ultrastructural study: alteration in neural architecture in diabetics
    - ◆ NOS
- historical/investigational studies

## Chapter 46 Questions - ED.doc

- ♦ penile brachial pressure index (PBI) = penile sBP/brachial sBP → poor sensitivity: do not use
  - ♦ normal flaccid penile sBP < 30mmHg below brachial sBP → measure w/ Doppler and pediatric cuff
  - ♦ PBI < 0.7 indicates arteriogenic ED
- ♦ penile plethysmography (penile pulse volume recording)
  - ♦ connect 2.5-3cm cuff to air plethysmograph
  - ♦ cuff inflated above sBP, then decreased by 10mmHg increments, get tracing at each level
  - ♦ pressure demonstrating best waveform recorded
  - ♦ normal waveform similar to arterial waveform
  - ♦ vasculogenic ED: slow upstroke, slow downstroke, low rounded peak, no dirotic notch
- ♦ biochemical studies
  - ♦ PGI<sub>2</sub>-TXA<sub>2</sub> ratio in penile blood during erection → lower in pts w/ arteriogenic ED
  - ♦ urinary metabolites of PGI<sub>2</sub> and TXA<sub>2</sub>

### What questionnaires exist for sexual function and ED?

- IIEF (International Index of Erectile Function)
  - 5 domains, 15 qns: sexual desire, erectile function, intercourse satisfaction, orgasmic function, overall satisfaction
  - most widely used, validated in > 7 languages
  - short form: IIEF-5
    - frequency of erection during sexual activity
    - frequency of erection sufficient for penetration
    - frequency of successful attempts at penetration
    - frequency of maintaining erection after penetration
    - frequency of maintaining erection until climax
- BMSFI (Brief Male Sexual Function Inventory):
  - sexual drive (2 qns), erection (3 qns), ejaculation (2 pts), perception of problems in each area (3 qns), and overall satisfaction (3 pts)
- Derogatis Sexual Function Inventory: 245 qns
- Center for Marital and Sexual Health Questionnaire: 18 qns
- EDITS (ED Inventory for Treatment Satisfaction)

### How can one differentiate b/w psychogenic and organic ED?

- Psychogenic
  - acute onset
  - situational dependent
  - varying course
  - rigid noncoital erection
  - long hx of psychosexual problems
  - partner problem at onset
  - prominent anxiety/fear
- Organic
  - gradual onset
  - global circumstances
  - constant course
  - poor noncoital erection
  - psychosexual problems secondary
  - partner problems secondary
  - anxiety/fear secondary

### How does one perform an ICI?

- Combined intracavernous injection and stimulation (CIS) test
  - full erection = adequate arterial and venous system → NPT sex therapy, or continue w/ ICI
  - sustained full erection after self-stimulation = adequate venous system → continue w/ ICI
  - partial erection after self-stimulation
    - apply vacuum device or perform 2<sup>nd</sup> ICI
      - ♦ good response → tx w/ ICI or vacuum device
      - ♦ poor response or rapid detumescence → consider prosthetic, get US Doppler scan
        - ♦ good artery → NPT, cavernosography, venous surgery
        - ♦ bad artery → get angio, arterial surgery

### When does nocturnal erection occur?

## Chapter 46 Questions - ED.doc

- 80% of NPT occurs during REM sleep
- average man has 2-3 episodes of NPT each night, each lasting up to 30-60min
  - age-specific variations: peaks at puberty

### What are the various ways of performing nocturnal penile tumescence testing?

- stamp test
  - ring of stamps placed around base of penis at night
  - if breaks, shows at least 1 episode of NPT had occurred
  - unreliable
- Snap Gauges
  - 3 different bands secured at base of penis, designed to break at 10, 15, 20 oz
  - false +ve results like stamp test due to movement during sleep, sabotaged by pts
- strain gauges
- NPTR (Rigiscan)
  - measures # of erectile episodes, tumescence (circumference), radial rigidity, and duration of nocturnal erection
  - recorded w/ EEG, EOG, EMG, nasal air flow, O<sub>2</sub> saturation to document REM sleep and sleep apnea
  - pt awakened to measure and photograph axial rigidity
    - Rigiscan measures radial rigidity exclusively → cannot measure axial rigidity
    - axial rigidity of 500-550g needed for vaginal penetration: 1.5kg considered maximal rigidity
  - can collect data for 3 separate nights for max 10hrs each night
  - device made of 2 loops, 1 at base and 1 at coronal sulcus → measures rigidity by constricting loops q3min
    - radial rigidity > 70% = non-buckling erection
    - radial rigidity < 40% = flaccid penis
- sleep lab NPTR
- NPT electrobioimpedance testing (NEVA device)
  - recording device attached to pt thigh, 3 small electrode pads attached to hip, base of penis, glans
  - determines volume by measuring impedance within penis
  - undetectable AC sent from glans to hip ground
  - as cross-sectional area increases w/ erection, impedance decreases

### What are the normal NPTR criteria?

- no accepted benchmarks
  - 4-5 erectile episodes per night
  - mean duration > 30min
  - increase in circumference > 3cm at base, > 2cm at tip
  - > 70% maximal radial rigidity at both base and tip
- criteria developed in young volunteers not applicable to aging potent male

### What physical factors regulate penile axial rigidity?

- intracavernous pressure
- penile geometry (diameter/length ratio)
  - short thick penis more resistant to buckling
- penile tissue mechanical properties (cavernosal expandability)
- **radial rigidity not an accurate predictor of axial rigidity**

### What are the indications for NPTR?

- abandoned for routine ED evaluation
  - suspected sleep disorder
  - obscure etiology
  - nonresponse to tx
  - planned invasive tx
  - legally sensitive case
  - measure of drug effect in RCT
  - suspected psychogenic etiology

### What is the definition of psychogenic ED?

- International Society of Impotence Research
  - persistent ability to achieve or maintain erection satisfactory for sexual performance due predominantly or exclusively to psychologic or interpersonal factors



## Chapter 46 Questions - ED.doc

### What is the role for neurologic testing in ED?

- will rarely change management
  - uncover reversible neurologic disease
  - assess extent of neurologic deficit from known neurologic disease: DM, pelvic injury
  - determine need for neurology referral: workup for possible cord compression

### What endocrinologic changes occur in the aging male?

- decrease in T
  - **MMAS: only 1 androgen decreases w/ age that is associated w/ ED: DHEA (and DHEAS)**
- flattening of circadian rhythm of FSH/LH
  - T secreted episodically in response to LH pulses, early morning peak (4am)
- increased levels of SHBG
  - T bound to SHBG is metabolically inactive
- decreased secretion of DHEA and DHEAS
- decreased production of GH
- decreased release of melatonin in response to darkness
- impaired thyroxine production
- increased levels of leptin
- no change in steroid or estradiol production

### What medications can inhibit T production?

- spironolactone
- chemo: MTX, alkylating agents
- ketoconazole
- metronidazole
- flutamide, other nonsteroidal antiandrogens
- cyproterone, other steroidal antiandrogens
- cimetidine

### What medications can inhibit GnRH release?

- progesterone
- estrogen
- GnRH agonists: leuprolide, goserelin
- increased PRL
- phenothiazines
- TCAs
- reserpine
- opioids
- cocaine

### What human tissues contain enzymes to convert DHEA to T by DHT?

- adipose, bone, muscle, breast, prostate, skin, brain

### What physiologic effects have been attributed to DHEA? (dose 25-50mg OD)

- therapeutic effect in DM
- protective effect against development of atherosclerosis
- decrease in chol, LDL, fat
- stimulates immune function
- stimulates brain function

### What are the limitations of PBI?

- measurement in flaccid state will not reveal full functional capacity of the cavernous arteries in the erect state
- errors from improper fitting of the BP cuff
- continuous wave Doppler does not select arterial flow from paired cavernous arteries → usually finds dorsal penile artery
  - normal PBI cannot be used to exclude arteriogenic ED

### What are the changes in Doppler waveforms and hemodynamic changes in the corporeal pressure after ICI?

- filling (latent) phase
  - low sinusoidal resistance (5 min), high forward flow during diastole

## Chapter 46 Questions - ED.doc

- tumescent phase
  - penile pressure increases, diastolic velocities decrease
- full erection
  - systolic waveforms sharply peak, may be less than during full tumescence
- rigid erection
  - cavernous BP may exceed systemic dBp w/ reversal of diastolic cavernous flow

### What are the different phases of detumescence?

- 1st: transient increase in intracorporeal pressure: indicates beginning of sm. muscle contraction against a closed venous system
- 2nd: slow pressure decrease, from slow reopening of venous channels w/ resumption of baseline arterial flow
- 3rd: fast pressure decrease, w/ fully restored venous outflow

### Describe the different phases of erection and detumescence, and the events in each phase.

| <i>Phase</i>           | <i>Arterial Flow</i> | <i>Intracorporeal Pressure</i> | <i>Veins/muscle</i>               |
|------------------------|----------------------|--------------------------------|-----------------------------------|
| • Filling              | low                  | low                            |                                   |
| • Latent               | rises                | low                            | high forward flow during diastole |
| • Tumescence           | decreases            | rises                          | emissary start to close           |
| • Full                 | low                  | rises                          | veins close                       |
| • Rigid                | none                 | peak (200-300mm)               | contraction of ischiocavernosus   |
| • Initial detumescence | small drop           | small rise                     |                                   |
| • Slow detumescence    | large drop           | drop                           | emissary veins open               |
| • Fast detumescence    | baseline flow        | rapid drop                     | normal venous outflow             |

→ mnemonic: Flaccid (limp) to full rigid is so fun

### What is the definition of cavernous veno-occlusive dysfunction (CVD)?

- inability to achieve and maintain erection despite adequate arterial inflow

### What findings on Doppler suggest venous leakage?

- excellent arterial response to ICI ( $> 30\text{-}35\text{cm/sec}$  PSV) + well-maintained EDV ( $> 5\text{-}7\text{cm/sec}$ ) + transient rigidity after self-stimulation
- RI (resistive index) =  $(\text{PSV} - \text{EDV}) / \text{PSV}$ 
  - as penile pressure approaches diastolic BP, diastolic flow decreases and  $\text{RI} = 1$
  - reversal of diastolic flow (-ve EDV) results in  $\text{RI} > 1$
  - $\text{RI} > 0.9$  associated w/ normal results in 90%
  - $\text{RI} < 0.75$  associated w/ venous leakage in 95%

### What are the options for nonsurgical treatment of ED?

- lifestyle changes: exercise, diet, stop smoking, moderate EtOH, stop long distance cycling
  - difficult to prove if beneficial
- changing medications
  - d/c antipsychotics, tranquilizers, antidepressants, antihypertensives (methyldopa, reserpine), central sympatholytics,  $\alpha$ -blockers,  $\beta$ -blockers, diuretics (thiazides, spironolactone), cimetidine, estrogens, antiandrogens
  - switch pts to newer drugs: CCB, ACEi → may reverse ED in some pts
  - try pts on trazodone if on antidepressants
- pelvic floor muscle exercises: use in pts w/ mild venous leakage
- psychosexual therapy: may work in some pts w/ organic ED by relieving anxiety
- hormonal therapy: refer pts w/ thyroid/adrenal/pituitary/hypothalamic dysfunction to endocrinologists
  - androgen therapy x 2-3months in pts w/ documented hypogonadism and ED → most pts have improvement in libido
- oral agents
  - Central conditioners: hormonal agents → act to improve CNS environment to promote erection
  - Central initiators: drugs w/ primary activity in CNS → initiate neural events, resulting in enhanced signalling for erection
    - centrally acting
      - ◆ yohimbine 5.4mg PO TID:  $\alpha_2$ -adrenergic blocker
        - ◆ acts centrally to promote sexual behaviour by blocking presynaptic autoreceptors and increasing adrenergic R activity
        - ◆ s/e: GI intolerance, palpitations, h/a, anxiety, agitation, BP increase
        - ◆ no efficacy over placebo
    - serotonergic agents

## Chapter 46 Questions - ED.doc

- ◆ trazodone 25-200mg: central initiator and peripheral conditioner
  - ◆ mild antidepressant w/ rare incidence of priapism
  - ◆ peripheral  $\alpha$ -blocker and central inhibition of serotonin reuptake (increasing 5-HT<sub>1c</sub>)
  - ◆ s/e: marked **sedation**, N/V, hypo/hypertension, retention, **priapism**
    - most people take advantage of morning sexual activity
- dopaminergic agonist
  - ◆ apomorphine 2-6mg
    - ◆ dopaminergic agonist, activating D<sub>1</sub> and D<sub>2</sub> receptors: not an opiate → dopaminergic stimulation is pro-erectile
    - ◆ acts in PVN, sexual arousal is necessary
    - ◆ rapid onset, mean time to erection 12min
    - ◆ 2hr window for sex, not affected by food
    - ◆ s/e: N/V (17%), dizziness (8%), sweating (5%), somnolence (6%), yawning (8%)
- Peripheral initiators: main site of action in penis to activate biochemical events that lead to erections
  - most available options: ICI, MUSE, topical, oral agents
  - adrenoceptor antagonists
    - ◆ phentolamine (Vasomax)
      - ◆  $\alpha_1$ -blocker, used in combination w/ papaverine for ICI, has been used PO as well
      - ◆ injection results in tumescence, but not rigidity
      - ◆ s/e: h/a, facial flushing, nasal congestion, increased brown fat tumours in rats
- Peripheral conditioners: act to improve local or systemic environments to enhance erection
  - PDE inhibitors
    - ◆ sildenafil citrate (Viagra) 25-100mg
      - ◆ selective inhibitor of PDE5, preventing the increase in intracellular Ca that causes smooth muscle contraction
      - ◆ s/e: small reduction in BP, h/a (16%), flushing (11%), dyspepsia (6.5%), nasal congestion (4%), visual changes (2.7%), diarrhea (2.6%), dizziness (2.2%), arthralgia (2%)
      - ◆ improved erection in 70% pts w/ htn, 56% w/ DM, 43% w/ RP (71% if bilateral nerve sparing), 80% w/ SCI
      - ◆ effects seen only w/ sexual stimulation, depend on intact cavernous nerve stimulation (w/ NO release)
        - would not see improvement in non-NS RP, or low SCI
      - ◆ takes 30-60min, slower if high-fat meal
      - ◆ metabolized by cytochrome P450 in liver
    - ◆ tadalafil (Cialis)
    - ◆ vardenafil (Levitra)
  - L-arginine 2800mg: to improve NO release pathway
    - ◆ 6/15 men improved in small study, vs. 0/15 on placebo
- intraurethral therapy (MUSE) 1mg → peripheral initiator
  - intraurethral alprostadil (synthetic PGE<sub>1</sub>)
  - stimulates adenylyl cyclase to increase intracellular levels of cAMP, lowering intracellular levels of Ca
  - drug transferred from urethra to sponge to cavernosum through venous channels
  - s/e: female vaginal discomfort after ejaculation, penile pain (33%), hypotension (1%), syncope (6%)
    - **must administer initially in office due to syncope**
  - results: 66% responded to in-office trial, 65% of which worked at home: 43% overall
- transdermal therapies: limited efficacy, + significant hypotensive s/e
  - nitroglycerin: smooth muscle relaxant
    - better erectile response than placebo
  - minoxidil (direct peripheral vasodilator): more effective than nitroglycerin
  - yohimbine ointment
  - PGE<sub>1</sub> gel (Topiglan)
- ICI
  - papaverine 20-80mg: alkaloid from opium poppy
    - PDE inhibition, leading to increased cAMP and cGMP in erectile tissue
    - papaverine also blocks voltage-sensitive Ca channels, preventing Ca influx
    - may also impair Ca-activated K and Cl channels
    - metabolized in liver, T<sub>1/2</sub> of 1-2h
    - advantages: low cost, stable at room temp
    - disadvantages: high incidence of priapism (0-35%) and corporeal fibrosis (1-33%), transaminitis
    - s/e: dizziness, pallor, cold sweats
    - initial dose in office: 2.5µg papaverine

## Chapter 46 Questions - ED.doc

- phentolamine methyrate (Regitine): competitive  $\alpha$ -adrenoceptor antagonist of  $\alpha_1$  and  $\alpha_2$ 
  - s/e: hypotension, reflex tachycardia, nasal congestion, GI upset
  - $T_{1/2}$  30min
- thymoxamine (Moxisylyte) 10-30mg: competitive  $\alpha_1$ -blocker
  - shorter duration of action (3-4h), some antihistaminic properties, fewer s/e, low incidence of priapism
- alprostadil (Caverject, Edex): synthetic PGE<sub>1</sub> 10-20 $\mu$ g
  - causes smooth muscle relaxation, vasodilation, inhibition of platelet aggregation by increased intracellular cAMP
  - 90% metabolized on first pass through lungs
  - higher response rate and lower incidence of fibrosis and priapism vs. papaverine
  - erections in 70-80%
  - s/e: pain at injection site (17%), hematoma (1.5%), priapism (1.3%), penile fibrotic lesions (2%)
  - considered drug of 1<sup>st</sup> choice for dx and management of ED in oral agent failure
- VIP 25 $\mu$ g: potent smooth muscle relaxant, used in conjunction w/ phentolamine
- calcitonin gene related peptide (CGRP): potent vasodilator
  - s/e: facial flushing and hypotension
- NO donors
  - linsidomine (SIN-1): antianginal drug that releases NO to stimulate production of cGMP and relax smooth muscle
    - ◆ can produce erection w/ minimal s/e w/ ICI in 69%, not as good as alprostadil
  - sodium nitroprusside 100-400mg: inorganic hypotensive agent that relaxes vascular smooth muscle w/ dilation of peripheral arteries and veins
    - ◆ effect in 1-2min,  $T_{1/2}$  2min → not as good as alprostadil
- vacuum constriction device

### What are the various androgen preparations available?

- Parenteral (esterified T): least expensive
  - testosterone enanthate (Delatestryl) 200-400mg IM q2-4wk
  - testosterone cypionate (Depo-Testosterone) 200-400mg IM q2-4wk
- Transdermal: more closely simulate normal circadian rhythms if apply patch in morning
  - Testoderm TTS 5mg patch to skin OD
  - Testoderm 4-6mg patch to scrotum OD
  - Androderm 2.5-5mg patch to skin OD: EtOH based gel breaks down epidermis to enhance transmission
  - Androgel cream 1%
- Oral: largely rendered inactive during "first-pass" circulation through liver → large doses hepatotoxic
  - testosterone undecanoate (Andriol) 120-160mg PO OD: relatively free of liver toxicity
  - methyltestosterone (Metandren) 10-30mg SL OD
  - fluoxymesterone (Halotestin) 5-20mg PO OD
  - methandrostenolone 5-10mg PO OD

### What are the adverse effects of androgen therapy?

- hepatic complications
  - hepatitis, cholestatic jaundice, hepatoma, hemorrhagic liver cyst, HCC
- suppression of LH and FSH production
  - infertility
  - breast tenderness
  - gynecomastia
- **erythrocytosis: most common lab alteration seen w/ long-term therapy** → follow CBCs
- CVS risks
  - increase in RBC mass
  - increased LDL, decreased HDL
  - increased TXA<sub>2</sub> and platelet aggregation
- prostate cancer?
  - doesn't induce risk in men w/ normal prostates
  - if in doubt, TRUS/bx prior to starting androgen tx

### What are the contraindications to androgen supplementation?

- prostate cancer
- breast cancer

## Chapter 46 Questions - ED.doc

### What conditions are associated w/ increased plasma levels of sildenafil?

- metabolized by cytochrome P450
  - age > 65
  - liver impairment
  - severe renal insufficiency
  - drugs that inhibit cytochrome P450 enzymes 3A4 and 2C9: cimetidine, ketoconazole, erythromycin

### What are the contraindications to Viagra?

- absolute contraindication: nitrates
- relative contraindications:
  - men w/ angina not on nitrates
  - CHF and low BP/blood volume
  - complicated multidrug antihypertensives
  - hx MI/stroke
  - life threatening arrhythmia in past 6mo
  - BP < 90/50 or > 170/110
  - CHF
  - unstable angina
  - retinitis pigmentosa

### What drug combinations have been used for ICI?

- papaverine 30mg and phentolamine 0.5mg: effective in 72-87%
  - better than either alone, works in different types of ED
  - prolonged erection in 1-23%, fibrosis in 1-16%
- papaverine 2.5cc (30mg/cc), phentolamine 0.5cc (5mg/cc), alprostadil 0.05cc (500µg/cc) → Triple-Mix
  - each has different mode of action
  - more effective in pts w/ severe arteriogenic or mild veno-occlusive disease
  - as effective as papaverine alone, much lower incidence of painful erection
  - reserved for men that have failed alprostadil monotherapy or have significant pain
- papaverine and alprostadil
  - better than alprostadil alone
- VIP 30mg and phentolamine 0.5-2.0mg
  - overall RR 84%
- papaverine, phentolamine, alprostadil, forskolin (Quadmix)
  - forskolin: naturally occurring substance from root of *Coleus forskohlii*
    - activates adenylate cyclase, increasing intracellular cAMP
    - works in 20% of men that fail Trimix

### What are the contraindications for ICI?

- sickle-cell anemia
- schizophrenia
- severe systemic disease
- anticoagulants: OK if compress injection site for 7-10min

### What factors affect efficacy of ICI in ED?

- nonvascular cause of ED → RR to ICI quite high: 80-100%
- length of use: improvement of blood flow after long-term ICI

### What are the reasons pts decline/stop using ICI?

- pain
- inadequate response
- fear of needle
- unnaturalness
- loss of libido
- loss of partner
- concomitant illness
- recovery of spontaneous erection
- choose other therapy

### What are the pros and cons of the vacuum device?

## Chapter 46 Questions - ED.doc

- Pros
  - produces erection in most pts sufficient for coitus
  - causes glans engorgement: can be used in pts w/ glanular insufficiency
  - can be used with pts that have malfunctioning penile prosthesis
  - can be used after explantation of penile prosthesis
- Cons
  - blood oxygen level less
  - portion of penis proximal to ring is not rigid: may pivot
  - penile skin cold/dusky
  - ejaculation may be trapped
  - ring may be painful
  - caution in pts that use ASA or coumadin

### What are the complications from the vacuum device?

- penile pain/numbness
- difficult ejaculation
- ecchymosis and petechiae, hematoma (10%)

### What are the results from using the vacuum device?

- satisfaction 68-83%
- 20% reject primarily, 30% after 4 mo

### What is involved in the evaluation of priapism?

- Hx
  - hx sickle cell, neurogenic, psychiatric disease
  - pain
- Px
  - corpora cavernosa: fully rigid in low-flow, semi-rigid in high-flow
  - glans not involved: rare to have tri-corporeal priapism
  - DRE
  - abdo exam
  - neurologic exam
- Labs
  - HbS to r/o sickle cell, r/o leukemia
  - cavernous blood gas: venous blood = low-flow, arterial blood = high-flow
- Imaging
  - <sup>99m</sup>Tc RBC scan: may differentiate high vs low flow → uptake high in arterial priapism, low in veno-occlusive type
  - duplex US of cavernous arteries
    - minimal arterial flow w/ distended cavernosa in low-flow
    - ruptured artery w/ pooling in high-flow

### What are the treatment options for priapism?

- Low-flow
  - aspiration of corpora
  - ICI w/  $\alpha$ -agonist: epi 10-20 $\mu$ g, phenylephrine 250-500 $\mu$ g, ephedrine 50-100mg
    - most effective, almost 100% effective if within 12h
    - none will respond if > 36hrs
  - irrigation w/ dilute  $\alpha$ -agonist solution
  - PO terbutaline: RR 36%
- Sickle-cell disease
  - occurs in 28% of all cases of priapism
  - aggressive hydration, oxygenation, metabolic alkalization to reduce sickling
  - super-transfusion and erythropheresis
  - irrigation and ICI
- Recurrent (stuttering) priapism
  - self-ICI w/ phenylephrine
  - use of **antiandrogen or GnRH agonist** to suppress nocturnal erection
- High-flow priapism
  - ice-packing: causes vasospasm and spontaneous thrombosis of ruptured artery
  - arteriography + embolization

## Chapter 46 Questions - ED.doc

- injection of methylene blue to counteract NO releases

### What are the complications of medical treatment of priapism?

- Early
  - acute htn, palpitation, cardiac arrhythmia from  $\alpha$ -agonists and bleeding
  - infection and urethral injury from puncture
- Late
  - skin necrosis
  - infections and abscess

### What are the complications of priapism?

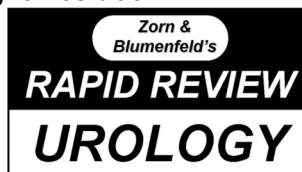
- fibrosis and ED
  - most pts regain potency if priapism stopped by 12-24h
  - after 36h, no pts respond to  $\alpha$ -adrenergic agents, all have some degree of fibrosis
  - high flow priapism: better prognosis, w/ ED rate 20%

### What are the AUA Guidelines for the management of priapism?

- Evaluation
  - Hx
    - duration of erection
    - degree of pain
    - previous priapism and tx
    - use of drugs that may have precipitated the episode
    - hx of pelvic, perineal, or genital trauma
    - hx of sickle cell disease or other hematologic abnormality
  - Px: genital, perineal, and abdominal exam: may reveal evidence of trauma or malignancy
  - Labs: CBC, retic count, Hgb electrophoresis, psychoactive medication screening, urine toxicology, blood gas testing, color duplex US, penile arteriography
    - cavernous blood gas: determine if ischemic or nonischemic
- Management
  - Ischemic priapism
    - treat all underlying disease (ex: sickle cell)
    - therapeutic aspiration +/- irrigation, or ICI w/ sympathomimetics/alpha agonist (ex: phenylephrine)
      - ◆ repeat as needed prior to surgical intervention
      - ◆ phenylephrine is alpha agonist of choice: dilute to 100-500ug/cc, inject q3-5min for 1hr before calling tx failure
      - ◆ children, pts w/ severe CVS disease require smaller volumes or lower concentrations
      - ◆ observe pts for s/e of these agents
      - ◆ BP/ECG monitoring are recommended in high risk pts
    - surgical shunt if ICI fails
      - ◆ Winters or Ebbenhøj, El-Ghorab, Quackel, Sacher
    - oral systemic therapy not recommended
  - Nonischemic priapism
    - corporal aspiration: diagnostic role only
      - ◆ ICI of alpha blockade not recommended
    - initial management is observation
      - ◆ discuss risk of spontaneous resolution, risk of tx-related ED, lack of significant consequences of delaying intervention
    - selective arterial embolization w/ autologous clot or absorbable gels (non-permanent)
    - surgery: last resort: perform w/ intra-operative color duplex US
  - Stuttering priapism
    - treat each episode as ischemic priapism
    - trials of GnRH agonists or antiandrogens may be used
      - ◆ should not use in pts w/o full sexual maturation or adult stature
    - consider ICI self-injection in pts that fail or reject systemic therapy







**Chapter 47**  
**• Surgery for ED •**

**What are the possible reasons for failure for revascularization procedures?**

- significant end-organ disease
- poor runoff after rearterialization for damaged arterial systems

**How does one counsel the pt for ED surgery?**

- discuss alternative nonsurgical treatment modalities
- choice of incision
  - subcoronal partial/complete circumferential: for semi-rigid devices
    - circ necessary to prevent edema, required to prevent infection if balanitis present
  - penile scrotal or infrapubic: for 2-3 piece inflatable prosthetic
    - easier to dilate intracavernous space
- what prosthetic does, where it is placed
- expected results, involvement w/ others w/ prosthetics
- complications: incidence, need for revision/removal, device longevity
- state all present erectile function is lost
- questions

**What are the different types of penile prosthetics available?**

- Semirigid: pure silicone or contain metallic core
  - Malleable
    - Mentor: Malleable, Accuform
    - AMS: 650, 600M
  - Mechanical: PTFE-coated interlocking polysulfone rings connected by spring-loaded cable: locks ring in column w/ activation, unlocks for flaccid state
    - TMT: Dura II
- Inflatable
  - 2-piece
    - AMS: Ambicor → pre-filled closed hydraulic system w/ tiny pump connected to cylinders
    - Mentor: Mark II
  - 3-piece: scrotal pump w/ SP reservoir
    - AMS: 700 CX, 700 CX pre-connected, 700 CXM, 700 Ultrex, 700 Ultrex Plus
    - Mentor: Alpha 1, Alpha 1 Narrow-Base, Alpha 1 w/ lock-out valve
      - ◆ lockout: designed to prevent auto-inflation by inhibiting fluid transfer from reservoir when not under demand by pump

**What are the considerations for selecting the appropriate device for the pts?**

- pt preference
- cost of device
- surgeons preference

**What are the advantages and disadvantages of the various types of prosthetics?**

- Semirigid
  - Advantages
    - easier placement
    - easier to use
    - less chance of failure due to wear
    - lower cost
    - more rigid cylinder: better to hold condom collection device
  - Disadvantages
    - more prone to cylinder erosion in pts w/ neurologic disease: lack of sensation
    - less concealability

## Chapter 47 Questions - ED Surgery + Peyronies.doc

- inability to change girth
- Inflatable
  - 2 piece
    - Advantages: easier placement than 3 piece
    - Disadvantages: less rigidity and change in girth compared w/ 3 piece
  - 3 piece
    - Advantages
      - ◆ concealability
      - ◆ larger change of girth, more closely mimic natural erection
    - Disadvantages
      - ◆ harder placement
      - ◆ more chance of failure due to wear: multiple mechanical parts
      - ◆ higher cost
      - ◆ difficulty to work scrotal pump in pts w/ arthritis

### Describe the technique of insertion of a penile prosthesis.

- Pre-op
  - pt preparation: ensure realistic expectations, understanding that all erectile function gone, need for future OR
  - supine, Foley (esp in pts w/ corporeal fibrosis, or pts that need SP reservoir)
  - prepare pt for diversion if previous hx perforation, severe intracorporeal scarring
- Procedure
  - incision: subcoronal vs. penile scrotal/infrapubic
  - expose tunica albuginea of penis on lateral surface of corpus cavernosum
  - corporotomy w/ 15 blade, extend w/ straight Mayo scissors for 2.5-4cm
    - subcoronal incision: corporotomy started 2-3cm from glanular edge, carried proximally toward crura
    - infrapubic incision: most proximal incision placed 6-7cm from crural end of the corpora
      - ◆ allows minimal extender use, ensures exit of the cylinder tubing in a more direct manner
  - dilation of the corporeal space
    - proximal dilation: place dilation tool towards crura, abut against ischial tuberosity in crural direction
    - distal dilation: keep tip of dilator lateral to prevent perf into urethra
  - corporeal closure sutures placed on either side of corporotomy
    - makes subsequent closure of corporotomy easier
    - less risky for perforation of inflatable prosthetic
    - not necessary for noninflatable cylinders: can place interrupted sutures over cylinder
  - corporotomy and dilation bilaterally prior to placement of cylinders
  - measurement of length of corporeal space
  - irrigation of corporeal space w/ antibiotic solution
  - place cylinders +/- rear-tip extenders
    - place crural end of cylinders 1st for semirigid devices
    - cylinder suture on Keith needle, inserted through glans
    - inflatable cylinders: direct exit at tubing site
  - placement of reservoir/pump or pump
    - space created in subdartos space w/ finger
    - irrigate space w/ antibiotic solution
    - place pump
  - placement of SP reservoir
    - space created behind rectus via midline vertical incision in rectus fascia
      - ◆ alternative: make reservoir space through external ring w/ long-nosed nasal speculum
    - reservoir introduced
    - fill reservoir, add 5cc more water than size of reservoir capacity, clamp tubing w/ shod
    - close rectus w/ 0 Vicryl
    - connect reservoir, pump
    - inflate and deflate pump many times
  - wound closed in several layers
- Post-op
  - no drain unless ++ bleeding: remove in 24-48 hrs
  - Foley out next day
  - infla te 4-6 post-op, trial of intercourse ☺

**What is the most likely site of intraoperative tunica perforation in penile prosthetic insertion?**

## Chapter 47 Questions - ED Surgery + Peyronies.doc

- proximal end, near ischial tuberosity

### What are the complications of penile prosthesis insertion?

- Intra-operative
  - crural crossover
    - easy to force small dilator through septum into contralateral cavernosa
    - remove cylinder and place rigid spacer into dilated corpus cavernosa, redilate
  - crural perforation: proximal vs. distal
    - distal perf on 1st side of dilation in virgin corpora: abandon and reschedule
    - distal perf on 1st side w/ hx previous perf or severe scarring: repair perf, SP vesicostomy or PU
      - ◆ post-op antibiotics + RUG
    - distal perf on 2nd side after atraumatic 1st side: controversial
      - ◆ place contralateral cylinder to prevent bilateral corporeal fibrosis
      - ◆ can place bilateral drains + round-the-clock irrigation w/ antibiotics → decreases fibrosis
    - proximal perforation
      - ◆ suture crus through separate perineal approach
      - ◆ artificial windssock repair
  - urethral perforation: abandon OR, place Foley x 5-7d
- Post-operative
  - infection: 1-9%
    - RF: SCI, DM, hx UTI, replacement device operation → no increased UTI if hx rads
    - usually in 1st 3 months
    - historical: immediate removal + reinsertion 3-6mo later → results in bilateral fibrosis and penile shortening
    - immediate replacement w/ new prosthetic + intracorporeal drain for 5-7d irrigation w/ antibiotics (2-7cc q4-6h)
  - mechanical complications
    - mechanical wear
      - ◆ reoperation for mechanical wear 5% by 5-10yrs
      - ◆ increased in pts w/ prosthetic problems
      - ◆ if need to replace part of a failed prosthetic > 5 yrs old, replace entire device
    - encapsulation and autoinflation: may prevent reservoir from fully filling, keeping cylinders inflated → hydraulically inflate cylinder to rupture encapsulation
    - tubing kinks: incise pseudocapsule around tubing
    - fluid loss: check connector sites, then cylinders near tubing attachment
    - cylinder aneurysm
  - problems w/ position
    - inadequate cylinder length → SST deformity (downward glans tilt)
      - ◆ place larger prosthetic or rear tip extender to support floppy glans
      - ◆ Ball procedure: hemicirc incision, dorsal plication suture in tunica albuginea just proximal to corona
    - high-riding pump
    - kinked reservoir neck
  - pain
    - DDx: infection, oversized cylinders, buckling of cylinders
  - urinary retention
  - cosmetics and size
  - pressure erosion: +/- bowel, bladder involvement
    - most common sites: distal cylinder, scrotal pump
    - usually due to loss of penile sensation or failure to keep prosthetic deflated when not in use
    - possible to repair primarily w/o removing device if no frank pus
      - ◆ distal corporoplasty to repair lateral impending erosion → reseat in more medial position under glans behind fibrotic sheath
      - ◆ scrotal erosion: transfer pump to opposite scrotum
      - ◆ proximal erosion: repair through perineal incision
    - urethral erosion: temporary urinary diversion (PU)
      - ◆ remove eroded cylinder and insert at later date
      - ◆ ensure opposite cylinder not involved: can keep in place to maintain penile length, remove if involved
  - penile necrosis → RF: DM, rads, vascular disease
    - remove prosthetic, debride all necrotic tissue, antibiotics, reconstruction after 4-6mo
  - reoperation
    - often need to select smaller cylinders
    - may require urinary diversion

## Chapter 47 Questions - ED Surgery + Peyronies.doc

- penile numbness more common
- 10-20X increased infection rates after reoperation

### What is the role of penile prosthetic w/ Peyronie's disease?

- use in pts w/ significant ED associated w/ Peyronie's disease +/- excision of plaque

### What are the principles of prevention of infections in prosthetics?

- short hospital stay
- eliminate all other sites of infection pre-op
- d/c indwelling catheters 2 weeks prior to surgery and diversion
- antiseptic shower 2-3d prior and morning of OR
- periop antibiotics
- shave immediately preop
- 10-15min scrub prep
- intraop sterile technique
- antibiotic wound irrigation and prosthetic soaking

### What are the various salvage techniques for penile prosthetics?

- new components in same spaces + drains
- new components in new site
- retention of some components of the device
- early replacement after local and systemic antibiotics over 3 weeks
  - +/- PU w/ repair of perf

### What are the components of Dabs antibiotic solution?

- 100cc NS
  - 500mg neomycin
  - 80mg gentamycin
  - 100mg polymyxin

### What intraoperative sequential irrigation protocol can be used for salvage replacement of infected prostheses?

- kanamycin 80mg/L + bacitracin 1g/L
- ½ strength H<sub>2</sub>O<sub>2</sub>
- ½ strength povidone iodine
- pressure irrigation w/ 5L NS + 1g vanco + 80mg gent
- ½ strength povidone iodine
- ½ strength H<sub>2</sub>O<sub>2</sub>
- kanamycin 80mg/L + bacitracin 1g/L

### What are the contraindications for immediate salvage of infected prostheses?

- necrotic infections
- rapidly developing infections
- erosion of cylinders
- ?visible pus

### What are the most likely sources of fluid leak?

- connector sites: most common
- cylinders: 2nd most common

### What are the results of insertion of penile prosthesis?

- pt and partner satisfaction 60-80%

### What are the requirements for successful vascular surgery for ED?

- discrete focal lesion on angio (esp in young pts w/ hx trauma) or faulty veno-occlusive mechanism determined by infusion pump
  - venous leak from corpora cavernosa
  - no massive venous leakage
- no DM or neurologic disease
- no tobacco use
- pt complaint of short duration erection w/ sexual stimulation

## Chapter 47 Questions - ED Surgery + Peyronies.doc

- failure to obtain erection w/ PO/ICI agents
- normal cavernous arteries on Doppler

### What are the options for penile vascular surgery for ED?

- inferior epigastric or saphenous vein as input
- microvascular surgery
- modified Michal procedure: distal or proximal end-end to dorsal artery or end-side dorsal artery
- modified Virag procedure: arterialization of isolated segment of deep dorsal vein
- Hauri procedure: arterialization of dorsal vein/penile artery fistula

### What are the principles of penile vascular procedures?

- Pre-op
  - GA, supine position
  - angio: necessary for selection of preferable recipient vessel
- Procedures
  - no single type of revascularization surgery that fits every case
  - incision
    - arterial surgery: lower abdo midline → allows harvesting of inferior epigastric artery
    - venous surgery: anterior scrotal/perineal surgery
  - +/- transection of fundiform and suspensory ligament
  - Arterial surgery
    - dissect inferior epigastric vessels as far distally as possible
      - ◆ ligate small branches near its origin
      - ◆ take vein with artery: too time consuming/not possible to separate artery and vein
    - prepare recipient vessel prior to transection of inferior epigastric
      - ◆ remove valves in deep dorsal vein w/ 2mm valvulotome
    - connect donor arterial vessel (usually inferior epigastric - can be saphenous connected to femoral artery) to dorsal penile artery
      - ◆ 8-0 to 10-0 monofilament vascular sutures
    - reanastomosis of base of penis to inferior periosteum
  - Venous ligation surgery
    - entire penis inverted into the wound
    - ligation of communicators identified b/w superficial and deep system
      - ◆ must use absorbable suture: pt can palpate nonabsorbable
    - release of suspensory ligament for proper exposure for more distal deep dorsal vein and cavernosal vein (if present)
    - incision in Buck's directly over deep dorsal vein
      - ◆ ligation of vein on penile shaft
    - distal dissection of penile vein in midpenile shaft
      - ◆ stay in midline over deep dorsal vein to avoid injury to dorsal penile arteries and nerves
    - ligate all direct communicators from circumflex vessels
    - bipolar cautery only
    - cavernosometry to ensure adequate veno-occlusion present
    - resuspend penis to pubis
    - drain in infrapubic region

### What are the complications of penile vascular surgery?

- penile edema
  - elastic dressing for 24h to control
- ecchymosis and bruising, hematoma
- penile numbness: 20%
  - usually returns 12-18mo post-op
- penile shortening from scar entrapment
  - may require Z-plasty and scar release
- glans hyperemia
  - occurs during penile dorsal vein arterialization, when deep dorsal vein to glans in distal dissection is missed
  - re-explore and ligate arterialized communicator

### What are the results after vascular surgery for ED?

- Veno-occlusive surgery

## Chapter 47 Questions - ED Surgery + Peyronies.doc

- not agreed if is an effective treatment
  - veno-occlusion dependent on arterial inflow
  - controversy as to type of test to diagnose
  - variable surgical approach
- excellent (10-60%), improved (10-40%), late failure (15-50%), failure (10-60%)
- Arterial surgery
  - success in 40-80%, improvement in 15-30%

### What are the options for surgery for priapism?

- Winter (or Ebbenhoj) shunt
  - transglanular to corpus cavernosal 11-blade scalpel (Ebbenhoj) or needle core biopsy (Winter)
- El-Ghorab procedure
  - transverse glanular incision, rongeur to excise distal cavernosae
- Sacher procedure (Quackel x 2)
  - bilateral cavernosum and spongiosum shunts created
  - perineal approach
  - anastomoses at different levels to avoid urethral stricture

### What conditions have been associated w/ Peyronie's disease?

- Dupuytren's contracture: 30-40% of men w/ Peyronie's
- plantar fascial contracture (Lederhose's disease)
- tympanosclerosis
- external trauma to penis
- DM
- gout
- Paget's
- use of  $\beta$ -blockers
- use of phenytoin
- ICI
- urethral instrumentation

### What is the incidence of Peyronie's?

- 1% overall
- average age of onset 53 yrs

### What is the mechanism of injury during buckling trauma of the penis?

- most pts w/ Peyronie's have lesions dorsally
- acute Peyronie's
  - tunica is bilaminar on dorsum: bending of erect penis out of column produces tension on the outer strands of the septum, delaminating the layers of the tunica albuginea
  - bleeding occurs and space fills w/ clot
  - scar generated becomes Peyronie's plaque
- chronic Peyronie's
  - less turgid erections allow flexion of penis during intercourse, producing elastic tissue fatigue
  - further reduction in elasticity of the tissue, leading to multiple smaller ruptures of the fibers of the tunica w/ smaller collections of blood

### What is the natural hx of Peyronie's?

- active phase
  - painful erections and changing deformity of the penis
- quiescent phase
  - stabilization of the deformity, w/ disappearance of painful erection
  - 1/3 of pts present w/ sudden development of painful deformity

### What is the typical presentation of Peyronie's?

- Hx
  - penile pain w/ erection
    - usually resolves as inflammation improves
  - penile deformity
  - shortening w/ and w/o erection

## Chapter 47 Questions - ED Surgery + Peyronies.doc

- notice of plaque or indurated area in penis
- erectile dysfunction
- Px
  - well-defined plaque or area of palpable induration
    - usually on dorsal penis

### What is involved in the workup of Peyronie's?

- Hx
  - sx as above
  - mode and onset
  - prior penile surgery
  - instrumentation/trauma
  - hx fibromatosis
- Px
  - photographs of erect penis
  - examine penis on stretch
  - examine hands, feet, ears → r/o tympanosclerosis, contractures
- Ix
  - vascular testing: not defined

### What are the possible treatment options for Peyronie's disease?

- Medical
  - vitamin E (tocopherol) 800-1000 u/day
    - antioxidant: safe, cheap, and might work
  - Potaba (potassium aminobenzoate) 3g PO QID
    - single small blinded study (1978)
    - poorly tolerated, expensive → not advocated
  - tamoxifen 20mg PO BID
    - facilitates release of TGF- $\beta$  from fibroblasts
    - no advantage in small RCT
  - terfenadine (Seldane), fexofenadine (Allegra) 60mg PO BID
    - nonspecific antihistamine, well tolerated
  - colchicine 0.6mg PO TID w/ meals
    - 4 actions:
      - ◆ binds tubulin, causing it to depolymerize: inhibits motility and adhesion of WBC
      - ◆ inhibits cell mitosis by disrupting spindle cell fibers: acts as anti-inflammatory
      - ◆ blocks lipoxygenase pathway of arachidonic acid metabolism
      - ◆ interferes w/ transcellular movement of procollagen
    - well tolerated: diarrhea in 1/3
    - cheap
  - NSAIDs
  - steroids → intralesional injection: significant s/e, inconsistent improvement → don't use
  - CCB: verapamil
    - intralesional injection: no blinded studies show it works
  - collagenase: on study only
  - IFN: don't use
- Surgical
  - must have stable and mature disease to be a surgical candidate
    - wait 12-18mo from onset of disease w/ > 6mo of disease stability
  - Plication procedures
    - excision and plication of tunica opposite lesion
    - dorsal plication of tunica opposite lesion (w/o excision)
  - Incision/excision of plaque + graft
    - temporalis fascia, tunica vaginalis, tunica vaginalis island flap, vein graft, de-epithelialized penile skin, dermal graft
    - nonautologous grafts (Silastic, Gore-Tex, Dacron) → poor results

### Describe the procedure of dermal graft for Peyronie's disease.

- Procedure
  - incision: dependent on location of lesion

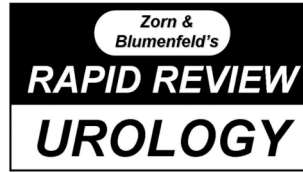
## Chapter 47 Questions - ED Surgery + Peyronies.doc

- ventral plaques: midline incision of ventral aspect of penis
- dorsal plaques: circumferential incision
- previous circ: use old circ scar
- deglove penis to its base
  - proximal plaques: 2nd incision on scrotum, lateral to base of penis
    - ◆ lay skin aside, cover w/ warm sponge
- elevate dorsal NVB w/ Buck's fascia
  - incise just lateral to spongiosum, w/ Buck's and dorsal NVB dissected off lateral and dorsal corpora cavernosa
  - alternate: dissect sharply through bed of deep dorsal vein, perform modified vein dissection
- artificial erection to define curvature
- place Prolene stay sutures in midline, proximal, and distal to plaque
- mark incision
  - if excision of plaque planned, incise tunica laterally to convert corporotomy defect from ovoid to stellate
    - ◆ releases tightness of defects edges
- excise plaque
  - measure defect: stretch penis to ensure adequate coverage
  - dermal graft outlined on donor site
    - ◆ graft site de-epithelialized, defat dermal graft
    - ◆ tailor graft to measure 30% larger in all dimensions
  - complete closure w/ 3-0 PDS, perform another artificial erection, oversee leaks
  - close penis, reappose Buck's w/ PDS
  - small suction drains
- alternate: H incision
  - flaps allowed to slide, leaving approximately square defect
  - graft sutured onto defect
- penis covered w/ Bioclusive dressing, mildly compressive Kling (x4h)
  - check glans q30min x 4h
- Postop
  - Foley x 1d
  - remove drains
  - suppress erections w/ Valium and amyl nitrate
  - after 2 weeks, encourage pts to have erections, but not sex
  - manipulate penis to prevent adherence of tissue
  - use vacuum device

### What are the complications of the Nesbitt procedure?

- penile edema
  - elastic dressing for 24h to control
- ecchymosis and bruising, hematoma
- penile numbness
- penile shortening
- ED





## **Chapter 48**

### **• Female Sexual Function and Dysfunction •**

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#### **What CNS pathways exist that control female sexual function?**

- sexual afferents enter cord in sacral segments
  - relayed to supraspinal sites via spinothalamic and spinoreticular pathways
  - fast myelinated fibers of spinothalamic path terminate in posterolateral nucleus of thalamus
  - spinoreticular fibers are slower: terminate in brain stem reticular formation
- spinal sexual reflexes under descending control from brain stem sites
  - nucleus paragiganticellularis projects to pelvic efferent neurons
  - PVN may control genital response

#### **What steroids hormones have been implicated in the sexual behaviour of women?**

- estradiol and related estrogens
- progesterone and other progestins
- testosterone and other androgens
  - 25% produced by ovaries (converted by androstenedione), 25% produced by adrenals, 50% produced by peripheral tissues (liver, skin, brain)
  - T replacement restores sexual desire after adrenalectomy and oophorectomy

#### **What are the different female sexual life phases?**

- Puberty
  - 1-3 yrs before males
  - 2 stages:
    - adrenarche: maturation of the adrenal cortex
      - ◆ from age 8-10, androgens derived entirely from adrenal cortex
    - menarche: heightened hypothalamic activity and increased LH secretion
  - average age of onset of menses: 12.6 yrs (range 9.1-16.2 yrs)
- Pregnancy
- Menopause
  - 4 general menopause-related changes in sexual function:
    - reduced sexual responsiveness, dyspareunia, decreased sexual activity, decreased sexual desire

#### **What are the different phases of the sexual response?**

- excitement
  - engorgement of the vaginal mucosa, causing thickening of the vaginal walls and transudation of fluid into the vagina
  - vasocongestion and engorgement
- plateau
  - labia minora become congested and enlarged
  - clitoris retracts under clitoral hood
  - lengthening of vagina, skin flush
- orgasm
  - peak of physiologic and psychological pleasure
  - rhythmic contraction of outer 1/3 of vaginal barrel, uterus
  - increase in BP, RR, HR, pelvic thrusts
- resolution
  - slow disappearance of pelvic and vulvar congestion
  - return of vulvar structures and breasts to normal size

#### **What is the definition of sexual dysfunction?**

- ICD-10: various ways in which an individual is unable to participate in a sexual relationship as he/she would wish
- DSM-IV: disturbances in sexual desire and in the psychophysiological changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty

## Chapter 48 Questions - F Sex Dysfn.doc

### How can one classify disorders of female sexual dysfunction?

- desire disorders
  - hypoactive sexual desire: persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts
  - sexual aversion: phobic aversion of sexual contact
- arousal disorder: inability to attain or maintain sufficient sexual excitement
- orgasmic disorder: difficulty in, or absence of attaining orgasm after sufficient sexual stimulation or arousal
- sexual pain disorders
  - dyspareunia: recurrent or persistent genital pain associated w/ sex
  - vaginismus: recurrent or persistent involuntary spasm of the musculature of the outer 1/3 of the vagina that interferes w/ sexual penetration
  - noncoital sexual pain disorder: genital pain induced by noncoital sexual stimulation

### What are the various etiologies of female sexual dysfunction?

- elderly
  - 11-48% have decline in desire, fewer sexual thoughts
  - problems w/ arousal/lubrication increase w/ age: less vaginal blood flow and genital engorgement
  - decreased blood flow causes increased vaginal pH: infections, dyspareunia
  - shortening of vaginal vault, decreased rugal folds, breast atrophy, thinning of vaginal mucosa
  - vaginal dryness, atrophic vaginitis
  - orgasm shorter and weaker w/ fewer contractions, may be painful
- cancer
  - depression, negative effect on body image → lack of desire
  - rads can cause vaginal atrophy, loss of elasticity, decreased vaginal length/caliber → dyspareunia
  - chemo: atrophic changes in vagina
- DM
  - metabolic problems can impact loss of desire
  - strong correlation b/w depression and sexual dysfunction in DM pts w/ neuropathy
- CRF
  - uremia impairs sexual desire in men and women
  - vascular insufficiency and autonomic neuropathy
  - steroids and antihypertensive agents affect desire
- IBD
  - abdo pain, diarrhea, fear of fecal incontinence cause lack of desire
- arthritis
  - RA associated w/ decreased sexual motivation, competence, decreased desire
  - impairs motion, making sex difficult/uncomfortable
- MS
  - decreased desire, spasticity, decreased orgasm
  - lack of vaginal lubrication, dyspareunia
- head injury
  - changes in sexual interest/desire are the most common sexual problem after head injury
- hypothalamic pituitary disorders
  - 80% have decrease in sexual desire
- depression
  - correlated to reduced sexual desire and arousal
- medications
  - tranquilizers decrease arousal and orgasm
  - hypnotics and sedatives decrease desire centrally
  - Li decreases desire
  - narcotics decrease desire
  - MAOI and TCAs prevent orgasm
- epilepsy
  - 14-66% of epileptics have low desire
- systemic sclerosis
  - vaginal dryness, ulcerations, and dyspareunia
- surgery
  - proctectomy: damage to pelvic nerves
  - posterior colporrhaphy
  - sacrospinous ligament fixation
- SCI

## Chapter 48 Questions - F Sex Dysfn.doc

- problems w/ lubrication
- 50% of SCI pts can have arousal and orgasm despite injury
- vascular causes: can affect orgasm
- TAH: can affect orgasm
- dyspareunia
- vaginismus

### How can one classify dyspareunia?

- insertional: pain localized to external genitalia and vagina
- deep: pain occurs inside pelvis w/ cervical movements and thrusting

### What are the causes of dyspareunia?

- physical causes: endometriosis, pelvic adhesions, pelvic tumours, abnormalities of the GI/GU tract, retroverted uterus, coital posture, intact hymen
- inflammatory causes: fissures at introitus, urethritis, vaginitis
- lack of lubrication
- psychological causes: anxiety, fear

### What are the options for treatment of FSD?

- problems w/ desire
  - steroids: for arthritis or other chronic disease
  - estrogens, progestins: restores vaginal lubrication
  - androgens: controversial
    - may enhance vaginal responsiveness
- problems w/ arousal
  - Viagra: RCT showed lack of efficacy in estrogenized women w/ sexual dysfunction
- problems w/ orgasm
  - adjustment of SSRI
  - sex therapy
- dyspareunia
  - fix reversible causes: vaginitis, endometriosis, anatomic abnormalities
  - estrogens and lubricants
  - HRT
- vaginismus
  - relaxation exercises
  - desensitization
  - Kegels
  - finger insertion
  - alteration of sexual position





## **Chapter 49**

### **• Normal and Anomalous Development of the GU System •**

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#### **Describe the development of the primitive kidney.**

- all 3 kidneys develop from primitive mesoderm
  - mesoderm on either side of midline differentiates into 3 subdivisions: paraxial (somite), intermediate, and lateral mesoderm
  - intermediate mesoderm separates from paraxial mesoderm and migrates toward coelom (future peritoneum)
  - mesoderm forms nephrogenic cords, bulging from posterior wall of coelomic cavity: forms urogenital ridge
- pronephros
  - first starts to appear late in 3<sup>rd</sup> week, disappears by 5<sup>th</sup> week
    - starts at cranial end of nephrogenic cord, progresses caudally
  - develop as 5-7 paired segments in the region of the future neck and thorax
  - rapidly degenerates along with segment of attached nephric duct
- mesonephros
  - mesonephric ducts begin to develop by 24<sup>th</sup> day as a pair of longitudinal tissue condensations parallel to nephrogenic cords
    - starts at 9th-10th somite levels
    - blind ends grow to primitive cloaca and contact it at 28<sup>th</sup> day
    - form a lumen at the caudal end, progresses cranially
  - mesonephric vesicles form soon after → completely gone by 4<sup>th</sup> month
  - vesicles form nephron, tuft of glomerular capillaries from branch of dorsal aorta invades the developing glomerulus
- metanephros
  - ureteric buds sprout from distal mesonephric ducts at 28<sup>th</sup> day
  - tip of dividing ureteric bud (ampulla) interacts with metanephric mesenchyme and induces formation of nephrons

#### **What elements of the mesonephroi are retained in mature GU system?**

- cranially located mesonephric tubules = efferent ductules of testis
- mesonephric ducts = vas and epididymis
- cranial and caudal mesonephric tubules = epoophoron and paroophoron

#### **What are the stages of the development of the renal collecting ducts, nephrons, and collecting system?**

- Stage I: metanephric mesenchyme forms vesicle separate from ureteric bud ampulla
- Stage II: vesicle forms S-shaped nephron that connects to ureteric bud
- Stage III: cup-shaped glomerular capsule matures into oval structure
- Stage IV: round glomerulus that resembles mature renal corpuscle
- Development of collecting system
  - by 6th week, ureteric bud has bifurcated 4 times, which coalesce to form 2-4 major calyces
  - by 7th week, next 4 generations of branches fuse, forming minor calyces

#### **Where are the most differentiated nephrons in the kidney?**

- older more differentiated nephrons are in inner part of kidney, newer less differentiated nephrons in periphery

#### **Describe the phenomenon of renal ascent.**

- between the 6<sup>th</sup> and 9<sup>th</sup> weeks, kidneys ascend to lumbar site just below adrenal
- differential growth of lumbar and sacral regions of embryo
- succession of transient aortic sprouts, degenerate and are replaced by successive new arteries
  - more inferior pair of arteries may persist as accessory lower pole arteries

#### **What is the role of WT1 and PAX2 in renal development?**

- WT1 (product of the Wilms' tumour suppressor gene) expressed in metanephric mesenchyme
  - lack of WT1 causes lack of ureteric bud formation and renal agenesis
- PAX2 is expressed in mesonephric ducts and ureteric buds

## Chapter 49 Questions - Embryology.doc

- inactivation causes lack of mesonephric duct, mullerian duct, ureteric bud and metanephric mesenchyme formation

### What is the role of GDNF (glial cell line-derived neurotrophic factor) and c-RET?

- GDNF secreted by the metanephric mesenchyme before ureteric bud formation
  - activates the c-RET receptor tyrosine kinase
  - inactivation results in renal agenesis or severe dysplasia
- c-RET expressed in ureteric bud
  - activation leads to induction of Wnt-11 and PGs, which lead to continued ureteric bud formation and branching
  - inactivation results in renal agenesis or severe dysplasia

### What other genes (and their products) exist that are important for mesenchymal differentiation?

- $\alpha 8\beta 1$  (integrin): in MM, lack causes renal agenesis/dysplasia
- WNT1 (glycoprotein): in MM, lack causes renal dysplasia
- BF2 (transcription factor)
  - induction signals from ureteric bud patterns mesenchyme into 2 cell populations: tubular and stromal
  - tubular cells directly contact ureteric bud, and express PAX2, SDC1, WNT4
  - BF2 expressed by stromal cell population
- BMP7 (TGF- $\beta$  class): in MM and UB, lack causes renal dysgenesis
- PDGFB (PDGF and ligand for R): in MM, lack causes absence of mesangial cells
- PDGFRB (receptor tyrosine kinase): in MM, lack causes absence of mesangial cells
- $\alpha 3\beta 1$  (integrin), in MM and UB, lack causes abnormal BM and glomerular podocytes

### What is the role of the RAS in the fetus?

- maintains the fetal GFR and to ensure an adequate urine output
- important for normal growth and development of ureter and metanephric kidney
  - kidney is able to produce all components of the RAS
  - both ANGII receptors (AT1 and AT2) expressed in developing mesonephros and metanephros
    - AT2 – produced in undifferentiated mesenchyme, modulates proliferation and apoptosis
      - ◆ expressed only in mesenchymal cells adjacent to stalk of ureteric bud
    - AT1 – produced in more differentiated structures, involved in renal vascular development

### What is the effect of ACEi given to pregnant mothers?

- increased rate of oligohydramnios, hypertension, anuria, increased rates of fetal loss

### What is the origin of the intrarenal vasculature?

- not completely understood: 2 theories
  - angiogenic hypothesis: derived exclusively from branches off the aorta
  - vasculogenic hypothesis: originate in situ within the embryonic kidney from vascular precursor cells

### What is the Weigert-Meyer rule?

- the upper pole ureteric orifice in a duplex system rotates posteriorly relative to the lower pole
- abnormally caudal upper pole orifice results from ureteric bud's arising too high on mesonephric duct
  - may drain to BN, verumontanum (into remnants of Wolffian ducts or into vaginal vestibule in girls)
  - vas may connect to ureter → leads to recurrent epididymitis/UTI, ipsilateral hydronephrosis

### Describe the development of the ureter.

- ureter starts as simple cuboidal tube, acquires lumen by 28 days
- may have transient ureteral obstruction between 37 and 40 days, recanalizes from midureter bidirectionally
- ureteral muscle starts at 12 weeks

### What is Chwalla's membrane?

- 2 cell-thick layer over the UO that is seen between 37 and 39 days duration

### What is meant by a CAKUT phenotype?

- Congenital Anomalies of the Kidney and Urinary Tract
  - UPJO, VUR, UVJO, MCDK, hypoplastic kidney, megaureter
  - seen in AT2 knock out mice

### Describe the formation of the bladder.

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- fetus lies within amniotic cavity, and yolk sac outgrowth forms the allantoenteric diverticulum in the connecting stalk that joins the fetus to the placenta
  - cloacal plate formed dorsal to connecting stalk
- fused area of endoderm and ectoderm = cloacal membrane → rotates to define cloaca behind it
- by 4<sup>th</sup> week, urorectal septum grows b/w allantoenteric duct and intestinal opening of cloaca
  - divides endodermal cloaca into UGS and hindgut (posterior anorectal canal)
  - partitioned by fusion of 2 lateral ridges of cloacal wall and descending urorectal septum
    - fold descends caudally: fold of Tourneaux
    - folds press in laterally: folds of Rathke → unite in midline
  - urorectal septum fuses w/ cloacal membrane to complete the separation of UGS and gut
- mesonephric duct contacts UGS by 24<sup>th</sup> day and divides cephalad *vesicourethral canal* from caudad urogenital sinus
- bladder is a simple tube of cuboidal cells at 10 weeks: apex tapers as urachus, continuous w/ allantois
- urachus involutes at 12 weeks, becomes the median urachal ligament
- acquires mature urothelial characteristics by 13<sup>th</sup>-17<sup>th</sup> weeks
- smooth muscle appears between 7<sup>th</sup> and 12<sup>th</sup> weeks: first at dome, then proceeding towards BN
- compliance is very low early on in gestation, increases gradually
  - may be due to changes in smooth muscle tone, CT composition, and mechanical factors from accumulating urine
- urethral sphincter develops in anterior wall of urethra

### Describe the formation of the trigone.

- common excretory ducts (mesonephric duct distal to ureteric bud origin) dilate by day 33, and are incorporated into the UGS
- R and L common excretory ducts fuse in midline as the trigone
- UO incorporated into the bladder by day 37, and is carried laterally and cranially by the developing trigone
- mesonephric duct orifice migrates caudally, parallel to the paramesonephric duct

### Describe the formation of the male and female internal genitals.

- during the 5<sup>th</sup> week, **primordial germ cells migrate from the yolk sac (allantois) along the dorsal mesentery** to populate the mesenchyme of the posterior body wall near the 10<sup>th</sup> thoracic level
- arrival of germ cells signals the adjacent coelomic epithelium to form genital ridges medial to the mesonephros
  - during 6<sup>th</sup> week, the cells of the genital ridge form primitive sex cords
- paramesonephric ducts form lateral to the mesonephric ducts via craniocaudal invagination of the coelomic epithelium
  - adhere to each other as they connect with the UGS
- Male
  - due to SRY, primitive sex cords change into Sertoli cells, form testis cords, and secrete MIS at 7-8 weeks
    - MIS causes (unilateral) degeneration of the Mullerian ducts between the 8<sup>th</sup> and 10<sup>th</sup> weeks
    - MIS is a member of the TGF- $\beta$  family: chromosome 19
  - Leydig cells differentiate from genital ridge cells by 9<sup>th</sup> – 10<sup>th</sup> week and secrete T
    - T detectable by 9 weeks
  - T stimulates mesonephric (Wolffian) ducts to transform into vas and epididymis
  - testis cords distal to seminiferous tubules develop a lumen, form rete testis, connect w/ efferent ductules
- Female
  - Sertoli cells do not form from SRY, MIS is not created, and Mullerian ducts do not degenerate
    - must have duplicate copies of at least one X chromosomal locus → dysgenetic ovaries in 45XO
  - T is not secreted and Wolffian ducts regress
  - estrogen detectable just after 8 weeks
  - primitive sex cords degenerate and mesothelium of genital ridges form secondary sex cords
  - primordial germ cells differentiate into oogonia
    - oogonia enter 1<sup>st</sup> meiotic division, then arrest until puberty
  - mesonephric ducts degenerate, paramesonephric ducts give rise to uterus and upper 2/3 of vagina
    - distal tips adhere to each other as they contact posterior wall of UGS
    - paramesonephric ducts form thickening at UGS called Mullerian (sinus) tubercle
      - ◆ forms tube w/ 1 lumen called uterovaginal canal
    - posterior UGS thickens, forming sinovaginal bulb, which gives rise to lower 1/3 of vagina
      - ◆ barrier persists between the most inferior portion of uterovaginal canal and UGS = hymen

### What are the origins of the seminal vesicles, prostate, and the bulbourethral glands?

- seminal vesicles sprout from distal mesonephric ducts, and prostate and bulbourethral glands develop from urethra at 10<sup>th</sup> week
- prostate development depends on conversion of T to DHT by 5AR

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### What are the Mullerian duct remnants in the male?

- appendix testis
  - appendix epididymis not Mullerian remnant: from cranial portion of degenerating mesonephros
- prostatic utricle - ?veru
- colliculus seminalis

### What is hernia uteri inguinale?

- males with persistent Mullerian duct structures

### What are the Wolffian duct remnants in the female?

- epoophoron
- paroophoron
- Gartner's duct cysts

### Describe the development of the external genitals.

- in 5<sup>th</sup> week, cloacal folds develop on either side of cloacal membrane, meet anteriorly to form genital tubercle
- genital tubercle appears by 6<sup>th</sup> week
  - divided by perineal body to form urogenital folds and anal folds
  - flanked by new swellings called labioscrotal folds
- cavity of UGS extends onto genital tubercle to form urethral groove during 6<sup>th</sup> week
  - flanked by urethral folds
  - temporarily filled by urethral plate, which disintegrates and recanalizes to form deeper secondary groove
- genital tubercle elongates to form phallus
- lower abdominal wall formed by further growth of mesodermal cells b/w the endoderm and ectoderm
- UGS separates into short tubular pelvic part and flattened phallic part
- Male
  - by 4<sup>th</sup> month, DHT causes fusion of labioscrotal folds in midline to form scrotum
  - urethral folds enlarge and fuse in midline to enclose penile urethra
    - 2 separate processes form urethra: fusion of urethral folds and ingrowth of ectodermal cells distally
  - corporal bodies differentiate from primitive mesenchyme that produced phallic growth
  - spongiosum and glans formed from caudal end of UGS and paired urethral folds
    - later become perforated from vascular passages that form erectile tissue
- Female
  - labioscrotal and urethral folds do not fuse, primitive perineum does not lengthen
  - phallus bends inferiorly, becoming the clitoris, and UGS becomes the vaginal vestibule

### Describe the phenomenon of gonadal descent.

- gubernaculum forms during 7<sup>th</sup> week
- processus vaginalis develops adjacent to inferior end (gubernacular bulb)
  - evaginates through transversalis (internal spermatic fascia), internal oblique (cremasterics) and external obliques (external spermatic fascia)
  - processus vaginalis degenerates: may occasionally remain patent, forming hydrocele/indirect hernia
- testicles descend to internal ring by 3<sup>rd</sup> month
  - complete descent by 7<sup>th</sup> to 9<sup>th</sup> month → rapid 2<sup>nd</sup> phase
- ovaries descend and are suspended within broad ligaments of uterus
  - gubernaculum becomes round ligament
  - causes ovaries to descend during 3rd month, places them within a peritoneal fold

### What theories exist to explain the mechanism of gonadal descent? (also see Chapter 67)

- active contraction by gubernaculum
  - genitofemoral n. supplies cremasterics – division in rats arrests descent
- gubernacular shortening through inguinal canal by rapid swelling at its base
  - enlarges inguinal canal
  - via increase in GAG and water, cellular hyperplasia and hypertrophy
- increased abdominal pressure
  - growth of abdominal viscera and fetal respiratory efforts
- GF nerve and CGRP
- epididymis



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### Where is the SRY?

- short arm of the Y chromosome

### What is the role of SF1 in gonadal development?

- SF1 (steroidogenic factor 1) catalyzes multiple steps in conversion of cholesterol to T
- SF1 knockouts fail to develop gonads
- expressed in Sertoli cells

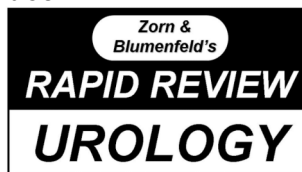
### What is the role of DAX1 in gonadal development?

- DAX1 knockouts causes CAH
- may function as an ovarian inducer
- SRY and DAX1 may act antagonistically

## DERIVATION OF REPRODUCTIVE TRACT STRUCTURES FROM WOLFFIAN (MESONEPHRIC) & MULLERIAN DERIVATIVES (Hinman Surgical Atlas)

| Male   | Female  |
|--|---|
| <b>Genital Ridges</b>  |   |
| Testis:  | Ovary:  |
| Seminiferous tubules (medulla)                                   | <i>Pfluger's tubules</i>                          |
| Rete testis  | <i>Rete ovarii</i>                                |
| <i>Gubernaculum testis</i>                                       | Round ligament of uterus                          |
| <b>Wolffian Derivatives</b>                                      |   |
| <b>Mesonephric Tubules</b>                                       |   |
| Ductuli efferentes   | Epoophoron  |
| Ductuli aberrantes   | <i>Ductuli aberrantes</i>                         |
| Paradidymis  | <i>Paroophoron</i>                                |
| <b>Mesonephric Duct</b>  |   |
| Kidney COLLECTING TUBULES, pelvis, ureter TRIGONE                | Kidney COLLECTING TUBULES, pelvis, ureter TRIGONE |
| Ductus epididymis  | <i>Duct of the epoophoron</i>                     |
| Ductus deferens  | <b>Gartner's duct</b>                             |
| Ejaculatory duct   |   |
| Seminal vesicle  |   |
| <i>Appendix epididymis</i>                                       | <i>Appendix vesiculosa</i>                        |
| <b>Mullerian Derivatives</b>                                     |   |
| <i>Appendix testis</i>   | Oviduct   |
|  | Uterus  |
| <i>Prostatic utricle</i>   | Cervix  |
|  | UPPER vagina                                      |
| Colliculus seminalis   | Hymen?  |
| <b>Urogenital Sinus Derivatives</b>                              |   |
| <b>BLADDER</b>   | <b>BLADDER</b>                                    |
| Urethra ABOVE COLLICULUS SEMINALIS                               | Urethra   |
| Urethra BELOW COLLICULUS SEMINALIS                               | LOWER vagina                                      |
|  | Vestibule   |
| MEMBRANOUS urethra   |   |
| **CAVERNOUS urethra  |   |
| **Bulbourethral (Cowper's) glands                                | Vestibular glands (Bartholin's)                   |
| **Prostate gland   | Paraurethral glands of Skene?                     |
| <b>External Genitalia (Genital tubercle, Genital swellings?)</b> |   |
| **Glans penis  | Glans clitoridis                                  |
| **PENILE urethra floor   | Labia minora                                      |

Vestigial structures in italics. (\*\*) = DHT-dependent.



## **Chapter 50**

### **• Renal Function in the Fetus, Neonate, and Child •**

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#### **When does urine production start in the human kidney?**

- 10 to 12 weeks

#### **Why does the fetus have low RBF?**

- decreased # of vascular channels early in gestation
- increased arteriolar resistance

#### **How do urine electrolytes change in the developing fetus?**

- Na excretion decreases w/ gestation
  - fetus produces large amounts of hypotonic urine with high sodium content and in large volumes
  - FENa has a -ve correlation with increasing age
  - blunted response to sodium loading: due to high levels of renin, ANGII, aldo, and decreased response to ANP
- K excretion increases w/ gestation
  - may be related to increased fetal plasma aldosterone concentration

#### **How does urine production change in the developing fetus?**

- increases from 5 cc/hr at 20 weeks to 50 cc/hr at 40 weeks

#### **What are the normal fetal urinary indices?**

- Na < 100 mEq/L
- Cl < 90 mEq/L
- osmolality < 210 mOsm/L
- urine total protein concentration < 20 mg/dL
- beta-2-microglobulin < 4 mg/L
- NAG (N-acetyl-D-glucosaminidase), fetal urine valine: should be low

#### **What is the definition of oliguria and polyuria in a newborn?**

- oliguria < 1 ml/kg/hr: virtually 100% of normal kids void by 24hrs
- polyuria > 2000mL/1.73m<sup>2</sup> daily: arbitrary limit

#### **What is the behaviour of renal blood flow at birth?**

- renal blood flow increases sharply at birth, due to:
  - redistribution of flow from inner to outer cortex
  - drop in renal vascular resistance associated w/ increased intrarenal PGs

#### **What causes the rapid rise in GFR seen in the first week of life?**

- diminished renal vascular resistance
- increasing perfusion pressure
- glomerular permeability
- increased filtration surface area

#### **When does GFR reach adult levels?**

- by age 2
  - serum Cr decreases by 50% in 1st week of life

#### **What electrolyte disturbance is common to premature infants?**

- infants < 35 weeks may develop hyponatremia if subject to sodium deprivation due to tubular immaturity and sodium wasting
  - Na supplementation needed in premature infants

## **Chapter 50 Questions - Fetal nephrology.doc**

### **What is the concentrating ability of the neonatal kidney?**

- can dilute fairly well, but has limited concentrating ability
  - immature renal medulla
  - decreased medullary concentration of Na and urea
  - decreased responsiveness of collecting ducts to ADH

### **How does the neonatal kidney respond to acid/base disturbances?**

- reduced threshold for bicarbonate resorption
- inability to respond to an acid load: premature kids often slightly acidotic

### **How does Ca/phosphate metabolism change after birth?**

- PTH is suppressed at birth
  - serum Ca falls
- causes increase in PTH
- tubular reabsorption of phosphate is high if premature

### **How does neonatal creatinine reflect renal function?**

- for 1<sup>st</sup> 48 hrs, plasma creatinine reflects maternal creatinine: must get serial values

### **How can one obtain a precise measurement of GFR in an infant?**

- DTPA scan
  - primary difficulty is obtaining accurately timed urine collection in incontinent pt w/o catheterization
    - GFR often under or overestimated by 100%
  - estimate of  $\text{CrCl} = k \times L / P_{\text{Cr}}$  (in ml/min/1.73m<sup>2</sup>)
    - k (constant): 0.33 preterm, 0.45 full-term, 0.5 children
    - L = length in cm

### **What is the normal 24hr sodium excretion in an infant?**

- 1-3 mEq/kg/day
  - fetus and neonate: accumulate sodium for growth
  - older infants and children: intake = excretion
  - renal losses ("salt wasting"): pts must increase sodium intake to compensate
- if > 3 mEq/kg/day = salt wasting
  - must improve diets

### **What is the role of the FENa?**

- used to isolate the tubular from the glomerular contribution to sodium excretion
  - can determine "prerenal" from "renal" or "postrenal" causes of oliguria
- $\text{FENa} = 100\% (\text{Una} \times \text{Pcr}) / (\text{Pna} \times \text{Ucr})$ 
  - $\text{FENa} < 2.5\%$  = prerenal in neonate, < 1% in older child
  - increased in sodium wasting
- better than measuring 24h Na excretion

### **What are causes of an increased FENa?**

- renal sodium wasting
- adrenal insufficiency
- SIADH

### **How can one classify RTA?**

- Type I: defective distal tubular acidification
- Type II: decreased threshold for proximal tubular bicarbonate resorption
  - intact distal tubular acidification
- Type III: combined proximal and distal abnormality
  - felt to be a variant of type ?
- Type IV: distal defect of impaired potassium secretion

### **What are potential sequelae of RTA?**

- growth retardation
- osteodystrophy
- nephrocalcinosis

## Chapter 50 Questions - Fetal nephrology.doc

- nephrolithiasis
- polyuria

### What is a normal urine pH?

- may vary from 4.5 – 8
- average 5.5-6.5
- 4.5-6.5 = acidic, 6.5-8 alkaline

### How can one evaluate RTA?

- get lytes, blood gas and urine pH
- determine if metabolic acidosis is present by measuring  $pCO_2$  on blood gas
- calculate anion gap: if elevated, consider ARF or ingestion of organic acids
  - if non-anion gap acidosis, ensure diarrhea not present
- obtain urine pH
  - **pH > 5.5 = Type I RTA**
  - **pH < 5.5**
    - **serum K elevated = Type IV RTA**
    - **serum K low/normal = Type II RTA**

### What are potential causes of RTA in children?

- congenital obstructive uropathy
- Fanconi's syndrome

### What investigations are needed in the workup of RTA?

- lytes, Ca, phosphate, PTH, thyroid function
- urinalysis
- 24h urine for CrCl, protein excretion, Ca excretion
- US abdo to look for nephrocalcinosis

### What is the treatment of RTA?

- initiate alkali therapy with  $NaHCO_3$
- HCTZ or Kayexalate if persistent hyperkalemia in type IV

### What are the causes of urinary concentration disorders in infants?

- renal maldevelopment
- AIN
- renal failure
- RTA
- sickle cell nephropathy
- medullary cystic disease

### What lab parameter will rule out an abnormality of urine concentration?

- urine specific gravity > 1.020 rules out serious abnormality

### What is the most common cause of hypercalciuria in neonates?

- administration of calciuric drugs: Lasix, glucocorticoids (used in bronchopulmonary dysplasia)
  - may be at risk for stone formation

### How is urinary calcium excretion determined in a neonate?

- Ca/Cr ratio (mg/mg)
  - normally < 0.2 in older child, < 0.4 in infant on breast milk, or < 0.8 in preterm infant

### What is the most common cause for glucosuria in hospitalized infants?

- IV glucose at rates > tubular reabsorptive threshold

### What are the complications in overhydration in an infant?

- opening symptomatic patent DA
- cerebral intraventricular hemorrhage
- necrotizing enterocolitis

## **Chapter 50 Questions - Fetal nephrology.doc**

### **What are the complications of underhydration in an infant?**

- hypoglycemia
- hyperbilirubinemia
- hyperosmolality

### **What is the effect of an ACEi on an infant GFR and why?**

- critical dependence of the fetal and neonatal glomerular capillary pressure on AT-mediated efferent arteriolar tone, fetal and neonatal GFR can drop precipitously after ACEi
- potency and duration of captopril greater in neonates than kids

### **What are the hemodynamic and renal effects of ANP?**

- ?opposite of ADH
  - increased GFR
  - natriuresis
  - diuresis
  - inhibition of RAS
  - vasorelaxation
  - increase in vascular permeability

### **What stimuli can increase ANP levels?**

- acute volume expansion
- intrauterine blood transfusion
- induction of atrial tachycardia
- fetal hypoxia

### **What happens to maternal PG levels during pregnancy?**

- increase successively during pregnancy
- PGs cross the placenta

### **What are the effects of maternal administration of NSAIDs during pregnancy?**

- can result in prolonged renal insufficiency and oliguria in the neonate

### **What is the effect of NO on renal function?**

- renal vasodilation
- regulation of tubuloglomerular feedback
- natriuresis

### **What is the effect of reduced functioning renal mass?**

- compensatory renal growth occurs prenatally
- compensation in neonate greatly exceeds that in an adult
  - neonate: hyperplasia and recruitment of unperfused nephrons
  - adults: cellular hypertrophy, increase in tubular volume

### **What is the effect of ureteral obstruction in midgestation vs. an obstruction occurring later?**

- ureteral atresia in early gestation results in irreversible multicystic dysplasia of ipsilateral kidney
  - maturing kidney more sensitive than adult kidney to injury from UO
  - injury may not be reversible with relief of obstruction
  - greater hemodynamic impairment of neonatal kidney
    - due to increased vascular resistance of immature kidney, increased activity of RAS
- obstruction occurring later (UPJO) causes less severe functional renal impairment

### **What is the renal response to perinatal hypoxia and ischemia?**

- renal vascular resistance increases
- GFR maintained: efferent arteriolar vasoconstriction
- neonatal kidney may be more susceptible to ischemia if superimposed hypotension

### **What is the fetal renal response to toxins?**

- developing kidney is more resistant to toxic agents
  - reduced perfusion of cortical nephrons

## **Chapter 50 Questions - Fetal nephrology.doc**

→ greater renal mass compared to body weight

### **What is the relationship of renal agenesis and renal insufficiency in adults?**

- congenital URA associated w/ FSGS and progression to renal insufficiency in adulthood
- > 25% of kids undergoing nephrectomy develop renal insufficiency and proteinuria in adulthood







**Chapter 51**  
**• Perinatal Urology •**

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**What is the normal appearance of the fetal kidney on US?**

- elliptical shape, distinctive internal echoes defined by medullary pyramids and peripelvic echo complex
- echolucent pyramids: can be confused for dilated calyces → appear at 20 weeks
- uniform echogenicity of renal cortex, slightly less than spleen or liver

**What are the potential abnormal findings on prenatal US, and their possible causes?**

- hydronephrosis/caliectasis/hydroureter: obstruction (UPJO, PUV), VUR
  - variation in degree of hydro during exam = VUR
  - dilated ureter best seen behind a full bladder
- abnormal AP diameter: increased in obstruction, VUR
- abnormal echogenicity: increased in dysplasia, obstruction, ADPKD
- urothelial thickening: variable w/ obstruction or VUR
- duplication → may be associated VUR or obstruction
- renal cystic structure: MCDK, ADPKD, duplication
  - single upper pole cyst is probably a dilated upper pole
- intravesical cystic structure: ureterocele
- urinoma: obstruction
  - urinary ascites may be noted in the fetus w/ severe obstruction → indicates a pop-off
- abnormal bladder filling: abnormal urine production
- abnormal bladder wall thickness: obstruction, neurogenic dysfunction
- "keyhole sign": PUV
- oligohydramnios: renal failure, obstruction
  - difficult to quantitate AF volume
  - shift from placental transudate to fetal urine after 16 weeks: most is urine by 20-22 weeks
  - may be difficult to diagnose oligohydramnios prior to 18-20 weeks

**How does one grade hydronephrosis in the fetus?**

- SFU (Society for Fetal Urology) consensus 1988
  - Grade 0: normal kidney with no hydronephrosis
  - Grade 1: slightly dilated renal pelvis without caliectasis
  - Grade 2: moderately dilated pelvis with mild caliectasis
  - Grade 3: large renal pelvis, dilated calyces, and normal renal parenchyma
  - Grade 4: very large renal pelvis, large dilated calyces, with thinning of the renal parenchyma > 50% of contralateral kidney

**What is the appearance on US of the following conditions:**

- UPJO
  - pelvic and calyceal dilation, without ureteral dilation
  - usually unilateral
  - ipsilateral ureter not visualized
  - bladder volume normal
  - amniotic fluid volume normal
  - renal parenchyma normal or only slightly thinned
  - perinephric urinoma
  - renal parenchymal cystic changes
  - parenchymal involution
  - M>F, L>R
- UVJO
  - variable dilation of renal pelvis and ureter to the bladder
  - may be greater dilation distally than proximally

## Chapter 51 Questions - Perinatal GU.doc

- VUR
  - variable dilation of collecting system: no way to diagnose on US only
  - may have increased renal parenchymal echogenicity
- PUV
  - bladder distension
  - bilateral hydro, associated w/ increased renal echogenicity
  - bladder thick walled
  - dilated posterior urethra
  - decreased AF volume: 2nd trimester oligohydramnios is usually lethal, due to pulmonary hypoplasia
  - perinephric urinomata
- ureterocele
  - upper pole hydro (or dysplastic upper pole) and dilated ureter traced to the bladder
  - intravesical thin walled structure associated w/ base of bladder
  - may have bilateral hydro if ureterocele causes BOO
- ectopic ureter
  - wall thickness of the ectopic ureter much greater than that of the ureterocele
    - ureterocele only made of attenuated ureteral wall, ectopic ureter made of bladder and ureteral wall
- MCDK
  - non-renaliform structure w/ multiple noncommunicating fluid-filled cystic spaces → only visible on real-time imaging
  - no central large cyst
  - minimal to no recognizable renal parenchyma
  - usually in normal renal position
  - differentiated from severe hydro by lack of central cystic structure w/ communicating dilated calyces surrounding it
- duplex system
  - usually have multicystic upper pole moiety
- ARPKD
  - large uniformly echogenic kidneys without recognizable cysts (too small to be seen)
  - oligohydramnios: most die of pulmonary insufficiency w/ Potter's
- congenital multilocular cystic nephroma
  - macrocysts
- renal agenesis
  - absence of AF after 16-18 weeks
  - adrenal glands visible in normal position: "lying-down" adrenal → linear appearance
  - small thorax
- bladder exstrophy
  - absence of bladder filling on repeated exam
  - low-set umbilical cord
  - abnormal appearing external genitalia
  - normal kidneys
- genital abnormalities
  - hypospadias, chordee may be seen
- neuroblastoma
  - seen as renal mass or suprarenal cystic mass

### What disorders are associated w/ fetal hydronephrosis?

- Down's syndrome: 3.3% incidence
  - do amnio for karyotype

### What is the most common renal mass seen on fetal US?

- congenital mesoblastic nephroma
  - replaces entire kidney w/ homogenous mass
  - remove postnatally
  - no need for early delivery

### How does congenital obstruction affect the developing kidney?

- smaller than normal
  - may be due to decreased activity of growth factors, increased cell death
- change in differentiation of cells
  - leads to "dysplastic" kidney
  - may be due to alterations in cell-to-cell signalling

## Chapter 51 Questions - Perinatal GU.doc

- dependent on timing of obstruction
- increased activity of RAA system
  - may permit normal function of obstructed kidney by increasing glomerular blood flow
  - may permit stable growth and development
- injury response patterns
  - fibrosis: glomerulosclerosis or in interstitium → leads to functional impairment by disrupting normal cell-to-cell communication and fluid movement
    - TGF- $\beta$ : promotes tissue fibrosis, regulated by angiotensin → higher levels in obstructed kidneys
    - primitive interstitial cells remain in obstructed kidney → "activated fibroblasts"
  - inflammation, altered growth
- nephrogenic DI
  - lack of concentrating ability
- associated pulmonary hypoplasia
  - late-onset oligohydramnios not associated w/ pulmonary hypoplasia

### What is the incidence of fetal GU tract anomalies?

- 0.2-0.9% of all pregnancies
  - UPJO most common, then VUR, PUV, and megaureter

### What are the requirements for fetal intervention for obstructive uropathy?

- when the life of the neonate is at risk
  - oligohydramnios + presumed BOO
  - must be a reasonable chance that fetus will benefit from in utero decompression
- normal karyotype by amniocentesis
- no systemic anomalies (CNS, CVS, others)
- male fetus
- singleton
- noncystic kidneys
- favourable urinary indices
- informed consent

### Describe the technique of fetal intervention for BOO.

- double pigtail vesicoamniotic shunt
- placed under US guidance over introducing needle

### What are the outcomes after placement of in utero vesicoamniotic shunts?

- for pts w/ good prognosis, survival is improved w/ in utero shunting
- in children w/ poor prognosis, outcome is poor
  - survival is increased, but most pts have renal insufficiency, +/- pulmonary impairment

### What is the postnatal evaluation and management for the pt with bilateral hydronephrosis detected prenatally?

- immediate US evaluation if concerned about PUV
  - PUV: palpable mass, neonatal ascites, thick bladder wall
  - VUR, megacystis/megaureter: thin walled bladder
- VCUG
  - < 1 week if severe bilateral hydro, otherwise 1-2mo
- if PUV suspected, bladder catheter left in situ until definitive therapy
  - 5F feeding tube
- antibiotics started
- upper tracts may not drain well due to ureteral obstruction from thickened bladder wall
  - persistent hydro, increased Cr, and acidosis
  - institute definitive decompression by day 3-5: ureteral reconstruction or temporary diversion (ureterostomy/pyelostomy)

### What is the postnatal evaluation and management for the pt w/ unilateral hydronephrosis detected prenatally?

- rarely any indication for urgent postnatal studies when unilateral hydro identified prenatally (if contralateral N kidney)
  - intervention delayed for several weeks: oliguria of neonatal period may under-represent obstruction
- baseline Cr by day 1-2
- VCUG
- functional imaging if VUR present

## Chapter 51 Questions - Perinatal GU.doc

### What is the postnatal evaluation and management for the pt w/ renal cystic diseases?

- US abdo, VCUG
- DMSA to r/o MCDK: no uptake on DMSA

### What is Karoli's disease?

- hepatic and pancreatic cystic disease in ARPKD

### What neonatal urologic emergencies are associated w/ the following presenting signs:

- sepsis: BOO, VUR, megaureter, ectopic ureter, ureterocele, UPJO, infection → get C&S, US, VCUG
- hematuria: UTI, RVT → get C&S, US
- hypertension: RVT, RAT → get US, DMSA
- renal mass: hydro, ARPKD, MCDK, CMN, neuroblastoma, Wilms' → get US, CT/MR/DMSA
- renal failure: obstruction, sepsis, renal cortical necrosis, renal dysplasia → get C&S, urine lytes, US, DMSA/MAG3
- urinary ascites: obstruction → get US
- scrotal mass: torsion, hydrocele, tumour → get US

### What is the evaluation and management of the following GU emergencies:

- ambiguous genitalia
  - Hx: drugs taken during pregnancy, unexplained deaths
  - Px: phallic structure, scrotal structure, pigmentation, presence of gonads, abdo masses, DRE
  - karyotype, 17-ketosteroid, 17-hydroxyprogesterone → r/o CAH
  - US abdo to examine internal structures
- undescended testes
  - unilateral: nothing at birth
    - plan for tx at 9-12 mo
  - bilateral: r/o intersex condition → serum T/FSH/LH, karyotype
- large scrotum
  - Px: transillumination to r/o hydrocele +/- hernia
  - US
  - exploration to r/o infarcted testes, contralateral fixation
- circ injury
  - vaseline gauze dressing if minor
  - acute repair if urethral injury
  - preserve foreskin if possible
- hypospadias: nothing in newborn period → examine testes to r/o intersex
- epispadias: review and planning for surgical repair
- urethral duplication: temporary diversion if obstructed
- perineal mass in female → 4 major causes:
  - periurethral cyst: do I&D
  - imperforate hymen w/ hydrocolpos: do I&D
  - prolapsed ectopic ureterocele: I&D to allow reduction into bladder, institute temporary catheter drainage
  - urethral prolapse: topical measures (moisturizers, hot compresses, relief of straining, remove catheters)
- bladder exstrophy
  - assess genital structures, location of testes, size of bladder plate
  - renal US
  - protect bladder w/ plastic wrap (no Vaseline)
  - early closure planned
- patent urachus
  - US to r/o cystic urachus
  - VCUG to r/o associated bladder anomalies (obstruction)
- cloacal exstrophy
  - separation of GI and GU tracts (end colostomy)
- abdominal mass
  - Px: location, size, texture, mobility of the mass, plus other systemic anomalies
  - US: organ of origin, cystic vs. solid, GU tract
- cloacal anomaly
  - r/o obstructed urinary drainage (distension of vagina by urine)
  - decompress vagina: Foley or CIC
  - colonic decompression w/ transverse colostomy

## Chapter 51 Questions - Perinatal GU.doc

- precise definition of GU anatomy: endoscopy, contrast studies
- imperforate anus
  - US, VCUG
  - assess level of rectourethral fistula
  - diverting colostomy
  - US distal spine to r/o cord anomalies
- prune belly
  - monitor renal function w/ serial Cr
  - vesicostomy if poor renal function
  - orchidopexy
- MMC
  - baseline US and VCUG ASAP
  - start CIC
  - early anticholinergic therapy
- oligohydramnios: confirmation of diagnosis prior to pt death
- single umbilical artery: associated w/ increased GU anomalies in past → routine screening not justified
- sepsis
  - urine C&S, renal US, VCUG
  - start antibiotics
- absence of voiding
  - US to r/o full bladder by 24h
- hematuria
  - may be due to maternal hormonal withdrawal producing urethral bleeding
  - C&S, abdo US
- htn
  - renal scan, US, VCUG
- urinary ascites
  - US abdo

### What are the most common GU causes of abdominal masses in newborns?

- MCDK: 35%
- hydro: 20%
- UPJO: 10%
- PUV: 10%
- ureteral duplication: 6%
- ARPKD: 6%
- Wilms': 4%
- RVT: 3%

### What is the presentation and management of the pt w/ renal vein thrombosis?

- Sx: enlarged kidneys, hematuria, anemia, thrombocytopenia, hx prolonged delivery
  - causes impaired renal blood flow w/ low BP, polycythemia, and dehydration
- US: enlarged kidney, visible thrombus
- Tx: fluid resuscitate, correct lyte abnormalities
  - anticoagulation: controversial

### What are the RF for adrenal hemorrhage?

- prolonged labour
- birth trauma
- large birth weight
- RVT may be associated

### What is the presentation and management of the pt w/ adrenal hemorrhage?

- Sx: anemia, shock., abdo mass
  - gross hematuria: unusual
- US: echogenic suprarenal mass
  - peripheral eggshell calcifications develop by 1 week (vs. stippled calcification of neuroblastoma)
- Tx: supportive

### What is the presentation and management of the pt w/ renal artery thrombosis?

### **Chapter 51 Questions - Perinatal GU.doc**

- Sx: htn, hematuria, renal failure  
→ usually due to umbilical artery catheterization
- Tx: control htn, ?removal of nonfunctioning kidney



## **Chapter 52**

### **• Evaluation of the Pediatric Urologic Patient •**

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#### **How can one triage the pediatric urologic patient?**

- Emergencies
  - trauma, torsion, gross hematuria, UTI, MMC, intersex, CAH, PUV, prune-belly, exstrophy, imperforate anus, cloacal anomalies, abdominal pain, testicular masses, vaginal masses, suspected child abuse
- Urgent
  - gross hematuria outside newborn period, febrile UTI outside newborn period, inguinal hernia, priapism, stones, STD
- Semiurgent
  - postnatal evaluation of hydro, LUTS, hernia, FTT, amenorrhea in adolescent
- Routine
  - prenatal hydro w/o evidence of BOO, asymptomatic hydrocele, UDT, meatal stenosis, hypospadias, varicocele, microhematuria

#### **What is involved in the evaluation of the pediatric urologic patient?**

- Hx
  - "Why is the child here?"
  - direct hx towards children
  - FTT: may be due to UTI, RTA, DI, CRF
  - fevers, abdo pain, scrotal pain, rectal pain
  - LUTS: onset in relation to potty training, time of day
  - eating and drinking pattern, BM pattern
- Px
  - VS
  - General: edema, cyanosis, mottling, Mongolian spots, café-au-lait spots, abnormal hair/nails, large head, epicanthal folds, widely spaced eyes, micrognathia, preauricular pits, macroglossia (BWS)
  - Abdo: protuberancy, hernia, umbilical leakage, kidneys
  - GU: inguinal canal (silk glove sign), UDT, hydrocele, foreskin, hypospadias, megameatus, penis (length, webbed, concealed), varicocele, perineal exam (clitoral hypertrophy, hymen, vaginal d/c, urethral prolapse), signs of abuse, labial masses/adhesions/fusion
  - lower back: presacral dimpling, hair → spina bifida: get US spine
- Labs
  - urine: pyuria, hematuria
- Radiology
  - US abdomen
  - VCUG
  - RNC: 1<sup>st</sup> exam to screen sibs of refluxers, F/U for refluxers
  - CT abdo: if suspect stones
  - MR

#### **Why is ASA contraindicated in children and adolescents?**

- associated w/ Reye's syndrome
  - multisystem d/o that affects liver and brain: cause unknown

#### **What are the causes of FTT in children?**

- 0-3mo: psychosocial, infections, GERD, IEM, CF
- 3-6mo: psychosocial, HIV, GERD, IEM, milk intolerance, CF, RTA
- 6-12mo: psychosocial, delayed introduction of solids, GERD, intestinal parasites, RTA
- >12mo: psychosocial, GERD

#### **What is the meaning of pyuria in children?**

- defined as > 5 WBC/HPF for girls, > 3 WBC/HPF for boys

## **Chapter 52 Questions - Paeds GU Eval.doc**

- UTI can occur w/o pyuria, pyuria may be present w/o UTI  
→ nitrates and WBC usually +ve in UTI

### **What are the causes of hematuria in children?**

- UTI: 26%
- perineal irritation: 11%
- trauma: 7%
- meatal stenosis w/ ulceration: 7%
- coagulation abnormalities: 3%
- stones: 2%

### **What is the management of the child w/ hematuria?**

- Gross hematuria
  - Hx/Px, VS
  - Labs: urine C&S, CBC, Cr, C3, urine Ca/Cr
  - Radiology: US abdo
- Microhematuria
  - Hx/Px, VS, Labs, Radiology
  - + proteinuria
    - large amount protein: refer to nephro
    - small amount: repeat over 2-3 weeks
  - - proteinuria
    - repeat over 2-3 weeks, get C&S, refer





## **Chapter 53**

### **• Renal Disease in Childhood •**

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#### **What is important in a nephrology history and physical for a child?**

- Hx
  - fatigue, malaise, abdo pain, N/V
  - prior streptococcal illness: GN
  - viral illness + hematuria: IgA nephropathy
  - FHx
- Px
  - small stature, ht, wt
  - flank pain, abdo tenderness, renal enlargement, rash
  - edema: nephrotic syndrome
  - chest for fluid overload, murmur, gallops
  - BP

#### **What lab data is important to establish presence of renal disease?**

- hematuria, proteinuria
- CBC, lytes, Cr, BUN, C3, ANA, hep B, sickle cell prep, CrCl

#### **What are the causes of red urine mimicking hematuria?**

- Heme +ve
  - hemoglobinuria: hemolysis, sepsis, dialysis
  - myoglobinuria: ketoacidosis, myositis, trauma
- Heme -ve
  - drugs: sulfa, nitrofurantoin, salicylates
  - foods: beets, food colouring
  - metabolites: homogentisic acid, porphyrin

#### **Do people normally excrete RBCs?**

- Yes – rates of up to 50000 RBC/hr over 24h are normal.

#### **How do dipsticks test for hemoglobin?**

- pseudoperoxidase reaction in reagent strip, or test for intact RBC
- can detect insignificant physiologic amounts of RBC, requiring microscopic evaluation of every sediment +ve for RBC

#### **What is a significant amount of microhematuria?**

- > 5 RBC / HPF in spun specimen or > 2 RBC / HPF in unspun specimen

#### **What is the significance of RBC casts?**

- suggests glomerular disease in children

#### **What is the significance of RBC morphology?**

- RBC that are normal shape (crenated) indicate non-glomerular bleeding
- RBC that are dysmorphic are associated with glomerular bleeding
  - often see doughnut-shaped cell with cytoplasmic extrusions

#### **What are the indications for cystoscopy in children?**

- diagnosis/treatment of ureterocele, mass, etc.
- investigation of gross hematuria in face of all other studies being normal (US abdo, VCUG, C&S)

#### **What urine parameter can cause a falsely +ve dipstick reading for protein?**

- a strongly alkaline urine

## Chapter 53 Questions - Paeds Nephro.docology

### What is a normal urinary protein excretion vs. abnormal vs. nephrotic range proteinuria?

- normal range  $< 4 \text{ mg/m}^2/\text{hr}$
- abnormal between 4 and  $40 \text{ mg/m}^2/\text{hr}$
- nephrotic range  $> 40 \text{ mg/m}^2/\text{hr}$

### What is the significance of the urinary protein / urinary creatinine ratio?

- Upr/Ucr ratios correlate closely w/ timed quantitative urinary protein measurements
  - normal range b/w 0 and 20 mg of protein / mmol Cr (Upr/Ucr ratio of 0 to 0.18)
  - ratio of greater than 1.0 is nephrotic range

### What is the normal value for urinary calcium excretion in 24 hours for a child?

- $< 4 \text{ mg/kg}$

### What is the most common cause of gross hematuria in kids?

- 49%: UTI
- 4% renal parenchymal disease

### What is the algorithm one should go through for hematuria?

- check for heme + or heme -ve
- if heme +ve, look at RBC morphology
  - no RBC: hemoglobinuria or myoglobinuria
- check for and quantitate proteinuria
  - none/minimal protein: check family members
    - if repeatedly -ve, reassure
    - if +ve: sickle cell prep, RBUS, Ca/Cr ratio
  - high protein: CBC, lytes, albumin, chol, BUN, Cr, C3, C4, ASO, ANA, hep B serology, refer to Nephro

### What is the DDX of hematuria?

- Glomerular (dysmorphic RBC + RBC casts)
  - IgA nephropathy (Berger's disease): most common cause (30%)
  - Glomerulonephritis
    - 1°
      - ◆ Nonproliferative: minimal change, membranous, FSGS
        - ◆ should normally be inactive sediment, occasionally some hematuria
      - ◆ Proliferative: mesangial proliferative, post-infectious, RPGN (crescentic), diffuse proliferative
      - ◆ Crossover: membranoproliferative
    - 2°
      - ◆ collagen vascular disease (SLE): hx rash, arthritis
      - ◆ vasculitis (HSP)
      - ◆ Goodpasture's: hx cough, hemoptysis, bleeding tendency, microcytic anemia
  - SBE
  - sickle cell nephropathy
  - HUS
  - thin GBM disease
  - familial nephritis (Alport's syndrome): FHx hematuria, deafness
  - hep B associated GN
- Non-glomerular (eumorphic RBC, no casts)
  - Medical
    - hypercalciuria: immobilization, vitamin D intoxication, loop diuretics, idiopathic
    - nephrocalcinosis
    - exercise: may herald IgA nephropathy
    - cystic kidney disease (PCKD, MSK): FHx of renal cystic disease
    - papillary necrosis: in DM, blacks, analgesic abusers
    - vascular disease (renal artery thrombosis, AV fistulae, renal vein thrombosis): if hx dehydration, bruit, htn, a.fib
    - TTP
    - DIC
    - hemophilia, thrombocytopenia: FHx bleeding
    - hemorrhagic cystic disease
    - sickle cell disease (normal unless decreased oxygen tension)

## Chapter 53 Questions - Paeds Nephro.docology

- Surgical (Post-Renal)
  - nephrolithiasis
  - cystitis: hemorrhagic cystitis
  - trauma
  - tumour
    - ◆ TCC: renal pelvis, ureter, bladder
    - ◆ RCC, hemangioma

### What is the most common cause of hematuria with eumorphic RBC?

- hypercalciuria (30%)
  - present in 5% of healthy white kids

### What is the etiology of hematuria in hypercalciuria?

- irritation or actual tubular cell damage by calcium containing crystals

### How does one screen for hypercalciuria?

- use random Uca/Ucr ratio
  - ratio of  $> 0.21$  indicates hypercalciuria
- definitive dx of hypercalciuria by 24h urine collection
  - $> 4$  mg/kg/day is abnormal

### What is the management of hypercalciuria?

- depends on clinical sx
  - dietary measures: avoid Ca/Na excess, increase fluid intake
  - HCTZ if clinically significant stone disease

### What are the signs and symptoms of acute GN?

- edema, htn, oliguria, and presence of dysmorphic RBC and RBC casts

### What is the most common cause of GN in kids?

- post-streptococcal GN

### What is the most common cause of ARF in kids?

- HUS

### How does post-streptococcal GN present?

- edema, brownish cola-coloured urine 7-10 days after sore throat (or 21-30 days after streptococcal pyoderma)
- +ve ASO, decreased C3 titer

### What is the treatment of acute post-streptococcal GN?

- control of htn
- manage lytes and fluid balance
- treat functional renal impairment

### What is the prognosis of post-streptococcal GN?

- $> 90\%$  recover
- microhematuria and proteinuria may persist for 3-6 months
- proteinuria that persists for 12mo may require renal bx to assess damage

### What are the histologic findings in IgA nephropathy?

- mesangial deposits of IgA in renal biopsy tissue in absence of systemic disease

### What factors denote poor prognosis in IgA nephropathy?

- bx findings of glomerulosclerosis, severe mesangial proliferation, glomerular crescents, and interstitial fibrosis
- renal impairment, htn, male, older age

### What is the prognosis of IgA nephropathy?

- progressive renal failure in 30-50% in 10-20 years

### What is the treatment of IgA nephropathy?

## Chapter 53 Questions - Paeds Nephro.docology

- none

### What is HSP?

- Henoch-Schonlein purpura: a vasculitis seen in boys from age 2-11
- sx of nonthrombocytopenic purpura, colicky abdo pain, joint pain and swelling, and GN

### What is the prognosis of HSP?

- 50% of HSP pts that have nephrotic syndrome get ESRD in 10 years

### What is the treatment of HSP?

- renal biopsy to dx
- no tx, other than steroids (which don't really help either)
  - may help if soft tissue swelling, joint disease, scrotal swelling, colic or GI hemorrhage

### What is HUS?

- hemolytic-uremic syndrome is a heterogenous group of disorders
  - hemolytic anemia, thrombocytopenia, ARF
  - most common cause of ARF in kids
- diarrheal and non diarrheal forms
  - diarrheal form: most common, associated w/ *E.Coli* or *Shigella* toxins
  - nondiarrheal forms: related to infection w/ *S. pneumoniae*, viruses, AD/AR inheritance, malignancy, renal transplant, CSA, BCP, chemo

### What is the treatment for HUS?

- dialysis for renal failure, management of ARF, maintain Hgb, platelet transfusion, plasmapheresis

### What are the poor prognostic factors for HUS?

- nondiarrheal form of HUS, < 1 yr old, prolonged anuria, severe htn, severe CNS disease

### What is Alport's syndrome?

- consists of hereditary nephritis, high-frequency hearing loss, ocular abnormalities
- family hx of deafness and ARF
- leads to ARF in 2<sup>nd</sup> to 3<sup>rd</sup> decade of life

### What are the renal manifestations of SLE?

- minimal change disease, focal GN, diffuse proliferative GN
- hematuria/proteinuria almost always seen at diagnosis, 50% have nephrotic syndrome
  - 80% female, peak age 12 yrs

### What renal functional abnormalities are seen in pts w/ sickle cell?

- increased total RBF
- decreased flow in vasa recta
- decreased maximum urine osmolality in response to water deprivation
- abnormal lowering of urine pH in response to acid loading
- increased tubular secretion of uric acid

### What are the features of sickle-cell nephropathy?

- hematuria
  - dysmorphic RBC
  - M > F
- papillary necrosis
- glomerulopathy
- nephrogenic DI
- incomplete RTA
- hyperuricemia
- asymptomatic bacteriuria

### What is the treatment for sickle-cell nephropathy?

- bed rest, hydration, oxygen
- alkalization, aminocaproic acid, IV diuresis

## Chapter 53 Questions - Paeds Nephro.docology

### What are the possible causes of transient proteinuria?

- febrile illness, seizure, exercise, CHF, exposure to cold

### How does one test for orthostatic proteinuria?

- child voids at bedtime: discarded
- child voids before getting out of bed: specimen 1
- child voids later in day: specimen 2
- if specimen 1 is free of protein, and specimen 2 is +ve, orthostatic test is +ve

### How does one evaluate the child w/ persistent asymptomatic proteinuria?

- quantitate urinary protein excretion
  - timed urine sample: 12- or 24-hr collection
  - protein > 4 mg/m<sup>2</sup>/hr: abnormal
  - protein > 40 mg/m<sup>2</sup>/hr = nephrotic range proteinuria
- Upr/Ucr ratio: > 0.18 abnormal, ratio > 1.0 is nephrotic
- lytes, Cr, BUN, albumin, C3, urine C&S, RBUS
- renal biopsy if > 6-12 mo

### What is the definition of the nephrotic syndrome?

- edema, hypoalbuminemia (<2.5 g/dl), hypercholesterolemia, and proteinuria (> 40mg/m<sup>2</sup>/hr or Upr/Ucr > 1.0)

### What histologic patterns are seen with the nephrotic syndrome?

- minimal change, FSGS, MPGN, membranous GN, mesangial proliferative GN

### What indications for renal bx exist for pts with the nephrotic syndrome?

- younger than 1 yr, older than 10 yrs, low C3 level, +ve ANA, pt has +ve nephritic component

### What pattern of nephrotic syndrome can recur in transplanted kidney?

- FSGS

### What is the management of congenital nephrotic syndrome?

- renal bx if < 1yr, exclude syphilis
- IV albumin, bilateral nephrectomy, HD, early transplantation
  - does not respond to steroids
  - pts prone to pneumococcal sepsis, peritonitis, clotting abnormalities, malnutrition

### What are the sx of AIN?

- mild to severe renal failure, N or decreased u/o, mild hematuria, decreased urinary concentration, proteinuria, pyuria, WBC casts, eosinophiliuria

### What is the etiology of AIN?

- immune-mediated
  - sarcoid, anti-BM disease, Sjogren's, tubulointerstitial nephritis-uveitis syndrome
- drug related
  - antibiotics: methicillin, pen, amp, cephalosporins, sulfonamides, rifampin
  - NSAIDs: fenopren, naproxen, ibuprofen
  - diuretics
- infectious causes
  - streptococcal diseases, diphtheria, toxoplasmosis, brucellosis, syphilis, rickettsia, EBV

### What are the symptoms of nephrogenic DI?

- polyuria, polydipsia, irritability, poor feeding, poor wt gain, fever, dehydration
- nocturia, obstipation, enuresis, poor growth, retardation
- megaureter, hydronephrosis

### What are the 2 genetically recessive forms of NDI?

- X-linked gene encoding type 2 vasopressor receptor
- homozygous defects in AQP2 (chrom 12) for aquaporin

## **Chapter 53 Questions - Paeds Nephro.docology**

### **What are some secondary causes of NDI?**

- drug-induced: Li, tetracyclines
- analgesic nephropathy
- sickle cell
- hypokalemia
- hypercalcemia
- obstructive nephropathy
- renal dysplasia
- chronic hydro
- amyloid
- sarcoid
- chronic uremic nephropathy

### **What is the treatment for NDI?**

- HCTZ, amiloride

### **What is Fanconi's syndrome?**

- low serum  $\text{HCO}_3^-$ ,  $\text{K}^+$ , phosphate associated w/ glucosuria, aminoaciduria, hyperchloremic metabolic acidosis, rickets
- most common cause of Fanconi's = cystinosis (abnormal efflux of cystine from most cells)
  - acquired forms: exposure of heavy metals, antibiotics (gent, tetracycline, cephalosporin), ifosfamide toxicity, FSGS

### **What is Bartter's syndrome?**

- distal renal tubular syndrome due to disordered NaCl reabsorption
- characterized by hyper-reninemic hypokalemic metabolic alkalosis
  - sx usually due to hypokalemia: weak, fatigue, neuromuscular irritability, cramps, polyuria, polydipsia, FTT in infancy

### **What are the 3 types of Bartter's syndrome?**

- Type 1: neonatal Bartter's
  - defects at gene coding for renal Na-K-2CL cotransporter and ROMK channel
- Type 2: classic Bartter's
  - deletion/mutation for renal Cl channel gene
- Type 3: Gitelman's syndrome
  - defect in gene for thiazide-sensitive NaCl cotransporter

### **What is the tx for Bartter's?**

- KCl replacement + spironolactone/amiloride



## Chapter 54

### • UTIs in Infants and Children •

#### **Describe the epidemiology of pediatric UTIs.**

- < 1yr: M > F
  - uncircumcised boys: 10X risk of circumcised boys
  - 2.7% of M, 0.7% of F have had bacteriuria
- school age
  - 1-3% F
  - < 1% M
- sexually active F have more UTI than non-active

#### **What are the clinical manifestations of UTIs in children?**

- Sx
  - fever: fever present in 2/3 of kids w/ UTI, UTI present in 14% of kids w/ fever
  - vague, nonlocalizing in infants: irritability (55%), poor feeding (38%), vomiting (36%), diarrhea (36%), abdo distension (8%), jaundice (7%)
  - older kids: SP pain, intermittent voiding dysfunction, dysuria, UI
  - pyelo: F/C, flank pain, LUTS, nonspecific sx
- Signs
  - renal mass (XGP), SP/flank tenderness
  - r/o ectopic ureteral opening, ureterocele, urethral discharge
  - back scars, sacral fat pads, sacral dimples, pits
  - r/o abnormal testes, labial adhesions, vaginal abnormalities
- Urine
  - U/A: pyuria > 5 WBC/HPF, leukocyte esterase, nitrites
    - RBC: unreliable
    - nitrites: 1<sup>st</sup> morning urine should be used
    - urinary catalase: high false+ve rate
    - +ve WBC and nitrites w/ microscopic bacteria on R&M = 100% sensitivity for UTI, or 100% NPV if all -ve
  - R&M
    - identification of bacteria in urine: represents > 30000 bacteria/mL
  - urine C&S
    - 95% probability if colony counts > 10<sup>5</sup> on CIC/voided urine, any number on SP aspirate
- Labs to determine renal involvement: none reliable
  - CBC, ESR, CRP, urinary concentrating ability, tubular enzymes, IL6, urinary Ab
- Imaging: usually for pyelo
  - early renal cortical lesions from pyelo can be seen w/ DMSA
    - 50-86% of kids w/ febrile UTI have renal involvement on DMSA
    - 50% of these persist 2y later
  - IVP: usually normal
  - CT: lobar nephronia visible
  - US

#### **How may one obtain urine specimens in kids?**

- difficult to obtain good specimens
  - bagged specimen: worthless → reflects rectal flora
    - if -ve, may r/o UTI
  - MSU: in circumcised boy, older girl, older uncircumcised boy
    - may reflect periurethral and preputial organisms
  - CIC: discard first portion (urethral organisms)
  - SP aspirate: most reliable, skin contamination should be nil, no urethral organisms
    - 21-22G needle
- if suspect UTI in non-toilet trained child, only CIC or SP aspirate acceptable

## Chapter 54 Questions - Paeds UTIs.doc

### How can one classify UTIs in kids?

- initial (1<sup>st</sup>) infections
- recurrent infections
  - unresolved bacteriuria during therapy
  - bacterial persistence
  - reinfection

### What are the causes of unresolved bacteriuria during therapy?

- natural bacterial resistance to antibiotic
- development of resistance during therapy
- inadequate antimicrobial urinary concentration: poor renal concentration, GI malabsorption
- infection from multiple organisms
- infection w/ 2<sup>nd</sup> organism during therapy

### What are the potential sources of bacterial persistence in children?

- Renal
  - infection stones
  - MSK
  - papillary necrosis w/ infected necrotic papillae
  - infected nonfunctioning or poorly functioning kidneys or renal segments
- Ureteric
  - infected ureteral stumps after nephrectomy
- Bladder
  - infected urachal cyst
  - vesicoenteric fistula
- Genitals
  - VVF
  - infected urethral diverticulum or periurethral gland

### What urologic abnormalities cause bacterial persistence?

#### Mnemonic: PERSISTAANCC

- Prostatitis: chronic bacterial prostatitis
- Ectopic: ureteral duplication and ectopic ureters
- R: foReign bodies
- Sponge: MSK
- Infection stones
- Stumps: nonrefluxing infected ureteral stumps after nephrectomy
- Tics: urethral diverticulae and infected periurethral glands
- Atrophic: unilateral infected atrophic kidneys
- Abscess: perivesical abscess w/ bladder fistula
- Necrosis: papillary necrosis
- Cysts: infected urachal cysts
- Calyces: infected communicating cysts of the renal calyces

### What bacteria usually infect the GU tract in kids?

- *E. Coli*
  - specific serotypes associated w/ pediatric UTIs: O1, O2, O4, O6, O7, O75
  - most have both MRHA and P fimbriae

### What bacterial traits may increase virulence for the GU tract?

- pili/fimbriae
  - P-pili: terminal glycolipid of the human RBC P blood-group Ag is a R that binds P fimbriae
  - P-fimbriated *E. Coli* more likely to cause fever, may need longer antibiotic courses
- hemagglutination
  - pyelonephritogenic *E. Coli* cause mannose-resistant hemagglutination (MRHA) of human RBC

### What is the natural hx of UTIs in kids?

- unpredictable, not completely understood
  - 3% F, 1% M get UTI



## **Chapter 54 Questions - Paeds UTIs.doc**

- 17% of these get infection-related scarring
- 10-20% of those w/ scarring get htn
- rare child w/ htn → ESRD

### **Describe the pathogenesis of UTIs children.**

- fecal-perineal-urethral route w/ retrograde ascent
- ascent to kidneys
  - hematogenous dissemination: impaired immunity, staph infections, TB
- ureteral dilation in acute infection

### **What are the signs of pyelonephritis on IVP?**

- renal enlargement: related to inflammation and edema
- focal renal enlargement: lobar nephronia
- delayed excretion
- dilation of collecting system

### **What are the signs of pyelonephritis on US?**

- thickening of renal pelvis
- hypoechogenicity
- focal or diffuse hyperechogenicity
- ureteral dilation
- decreased perfusion on Power Doppler

### **What are the signs of pyonephrosis on US?**

- shifting fluid-debris levels w/ change in position
- persistent echoes from lower collecting system
- air in collecting system
- weak echoes from pus in dilated poorly transonic renal collecting system

### **What factors affect renal scarring after UTI in kids?**

- intrarenal reflux
  - compound papillae found more commonly at poles → renal scarring seen more often at poles
  - ducts open at R angles, rather than obliquely w/ simple papillae
- urinary tract pressure
  - renal scarring usually occurs only w/ VUR + infection
  - scarring w/o UTI only if abnormally high bladder and renal pressures
  - normal intrapelvic pressures found in adults may be abnormally high in neonates
- immunity
  - young kids have incompletely developed immune system
    - easier colonization of bladder and kidney
    - eliminate bacteria less efficiently
- age
- treatment
  - if tx started within 1<sup>st</sup> few days of infection, acute suppurative response to bacteria minimized, and scarring decreased
  - anti-inflammatory agents may decrease scarring
  - vague sx may delay treatment

### **How does renal scarring change over time?**

- scars usually found on 1<sup>st</sup> set of imaging
  - remain unchanged regardless of future course
- older kids (> 5 yrs) have less risk of scarring
  - may be vulnerable until puberty

### **How does scarring cause hypertension?**

- poorly understood
  - likely involves RAAS
  - plasma renin normally decreases w/ increasing age: in reflux nephropathy, will increase
- **htn occurs independent of degree of scarring**

## Chapter 54 Questions - Paeds UTIs.doc

### How does pyelo affect future renal function?

- some kids develop delayed htn and ESRD w/o further UTIs
  - presence of scarring is RF for further decrease in renal fn
  - 2 theories:
    - progressive renal damage from hyperfiltration
    - progressive chronic immunologic damage

- GFR in scarred kidneys is decreased
- GFR in smaller kidneys is decreased

### What problems have been associated w/ UTIs in kids?

- urinary tract abnormalities
  - obstructive abnormalities: 5-10%
  - VUR: 20-60% → no association b/w reflux and risk of bacteriuria
- recurrent UTIs
  - boys: 18% recur if < 1yr, 32% if older boy
  - girls: 26% recur if neonatal, 40% recur if outside neonatal period → usually in 1<sup>st</sup> 3 months
  - risk of recurrence proportional to # of previous infections:
    - 1 prev (25%), 2 prev (50%), 3 prev (75%)
- voiding dysfunction and constipation
  - nocturnal enuresis alone not associated w/ UTI, diurnal enuresis is

### What factors affect the risk of bacteriuria in children?

- Age
  - more common at extremes of life
- Scarring
  - presence of scarring is RF for further complications
  - ACE gene polymorphism (DD type) associated w/ increased risk of progressive renal failure
- Sexual activity: active women have more UTIs
- Colonization
  - periurethral: colonization of periurethral area w/ ++ bacteria during 1<sup>st</sup> few weeks, decreases during 1<sup>st</sup> year
  - preputial: colonization highest during 1<sup>st</sup> months after birth, decreases after 6mo, uncommon after 5 yrs
    - risk of UTI 0.1% in circumcised males, 1% in uncircumcised males, 0.5% in females
    - most during 1<sup>st</sup> 3 months of life
  - fecal: colonization in nursery
    - presence of lactobacilli
- Immune status
  - immune system incompletely developed, serum IgA lowest b/w 1-3 months
    - urinary IgA is monomeric in infants(vs. secretory form in adults)
  - duration of breast feeding: protective effect in 1<sup>st</sup> 6 mo
- Genetics
  - sex: more boys during 1<sup>st</sup> year, more girls after 1<sup>st</sup> year
  - race: blacks have fewer UTIs, less VUR, less reflux nephropathy
  - virulence factors
    - P fimbriae
  - other genetic
    - Lewis (a-b- or a+b-) blood type: 3X greater risk for recurrent UTI than Lewis (a-b+ or a+b+)
    - sisters of girls w/ recurrent UTIs have higher incidence
- GU abnormalities
  - VUR: no correlation b/w VUR and susceptibility to UTIs, may resolve spontaneously
  - Pregnancy + VUR
    - unclear if pregnant woman w/ VUR w/o predisposition to UTI at increased risk of morbidity
    - pregnancy does not cause VUR
  - Neurogenic bladder: elevated bladder pressures risk increased renal damage + secondary VUR
- Iatrogenic: catheter induced UTI

### How does one treat acute pediatric UTIs?

- depends on child's age and severity of illness
  - < 3mo
    - severely ill, flank pain, unable to take fluids, or immune compromised: IV amp/gent, ancef/gent, or 3<sup>rd</sup> generation
      - ◆ tobra/gent 2.5mg/kg q8h

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- ◆ ampicillin 12.5-25mg/kg q6h
- ◆ ceftazidime 30-75mg/kg q8-12h
- taking fluids, less sick: 3<sup>rd</sup> generation oral OD
- > 3mo
- febrile UTI: broad spectrum
  - ◆ quinolones not approved: cartilage toxicity in animal studies
- uncomplicated UTI: oral broad spectrum x 3-5d
  - ◆ ampicillin 12.5-25mg/kg q6h
  - ◆ amoxicillin 10mg/kg q8h
  - ◆ TMP/SMX 4 mg/kg q12h (> 2mo)
  - ◆ cephalexin 10mg/kg q6h
  - ◆ nitrofurantoin 1.5mg/kg q6h
- IV treatment until sensitivities available and child improved, can take fluids, sterile urine

### What are the indications for GU antibiotic prophylaxis?

- VUR
- unstable GU tract abnormality: partial obstruction
- recurrent UTI
- acute UTI, awaiting radiologic eval
- urethral instrumentation
- immunocompromised
- CIC + VUR?

### What medications are used for GU antibiotic prophylaxis?

- nitrofurantoin 1-2mg/kg/day (> 1mo)
  - low serum levels, high urine levels, minimal effect on fecal flora
  - s/e: acute allergic pneumonitis, neuropathy, liver damage → hemolysis in G6P dehydrogenase deficiency
- cephalexin 2-3mg/kg/day
- TMP/SMX 1-2mg/kg/day (> 2mo for SMX)
  - SMX cannot be used < 2mo → sulfa competes for binding sites on albumin, causes neonatal hyperbilirubinemia and kernicterus
- trimethoprim 2mg/kg/day (? > 2mo)
  - significant TMP-resistance
- amoxicillin 5mg/kg/day
- nalidixic acid: contraindicated in prepubertal children → cartilage erosion

### Describe the evaluation of the child w/ a UTI.

- 1<sup>st</sup> UTI
  - abdo US + VCUG: DMSA if abnormal
  - maintain child on prophylaxis until studies complete
  - surveillance, periodic VCUG/US
- recurrent UTI
  - RNC: more sensitive for VUR detection, but less anatomic detail
    - minor radiation exposure: 27-1000X less radiation vs. standard VCUG

### Describe the management of asymptomatic UTIs in children.

- Hx/Px
  - often have sx when interviewed: enuresis, squatting, urgency, hx UTI
- manage UTI as any other

### Describe the treatment of recurrent UTIs in kids w/ normal GU tracts.

- prophylactic antibiotics if frequent UTI over limited period
  - 3-5 d acute tx
- observe for change in voiding patterns
- anticholinergic for incontinence
  - r/o tethered cord if acute incontinence in previously continent child
- bladder retraining: timed voiding, biofeedback
- treat constipation

### What is the etiology of acute hemorrhagic cystitis in children?

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- adenovirus 11
- BK: is a polyomavirus associated w/ hemorrhagic cystitis in immunosuppressed and BMT pts

### What is the etiology of epididymo-orchitis in children?

- young boys: often related to GU abnormalities or systemic hematogenous dissemination than in older boys  
→ *Haemophilus influenza* type b
- older boys: STDs: gonorrhoeae, chlamydia

What are the RF for funguria in children?

- antibiotics
- prematurity
- IV or umbilical artery catheterization
- TPN
- immunocompromised

### How can one estimate GFR in children?

- Cr cannot give same estimation as in adults: Cr changes w/ age and size  
→  $GFR = 0.55 \times ht \text{ (cm)} / Cr \text{ (mg/dL)}$



## Chapter 55

### • Anomalies of the Upper Urinary Tract •

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#### How can one classify renal and ureteral anomalies?

- Anomalies of **number**
  - Agenesis: bilateral, unilateral
  - Supernumerary kidney
- Anomalies of **volume and structure**
  - hypoplasia
  - multicystic kidney
  - polycystic kidney: infantile vs. adult (ARPKD vs. ADPKD)
  - other cystic disease
  - medullary cystic disease
- Anomalies of **ascent**
  - simple ectopia
  - cephalad ectopia
  - thoracic ectopia
- Anomalies of **form and fusion**
  - crossed ectopia +/- fusion
    - unilateral fused kidney (inferior ectopia)
    - sigmoid or S-shaped kidney
    - lump kidney
    - L-shaped kidney
    - disc kidney
    - unilateral fused kidney (superior ectopia)
  - horseshoe kidney
- Anomalies of **rotation**
  - incomplete
  - excessive
  - reverse
- Anomalies of **renal vasculature**
  - aberrant, accessory, or multiple vessels
  - renal artery aneurysm
  - AV fistula
- Anomalies of the **collecting system**
  - calyx/infundibulum
    - calyceal diverticulum
    - hydrocalyx
    - megacalycosis
    - unipapillary kidney
    - extrarenal calyces
    - anomalous calyx (pseudotumour of kidney)
    - infundibulopelvis dysgenesis
  - pelvis
    - extrarenal pelvis
    - bifid pelvis

#### What is the incidence of bilateral renal agenesis (BRA)?

- rare: only 500 cases in literature
  - 23.5 per 100000
- genetic predisposition
  - 75% males
  - sibs/parents of index case: 4.5% have unilateral renal agenesis, 3.5% have BRA

## **Chapter 55 Questions - Renal anomalies.doc**

### **Describe the embryology of BRA.**

- complete differentiation of metanephric blastema occurs b/w 5th and 7th weeks
- requires presence and orderly branching of ureteric bud
  - ureteric bud arises from mesonephric duct
- absence of nephrogenic ridge or failure of ureteric bud to develop will lead to renal agenesis
  - BRA requires common factor causing renal or ureteral maldevelopment on both sides of midline
  - with complete absence of ureter, rudimentary kidney found in only a few instances

### **What are the anomalies associated w/ BRA?**

- GU
  - complete ureteral atresia > 50%
  - trigone poorly formed
  - hypoplastic bladder: due to lack of urine
  - penile agenesis
  - hypospadias
  - undescended testes
  - "lying down" adrenals → normal position
- low birth weights
- oligohydramnios
- characteristic facial appearance (Potter's facies)
  - "prominent fold of skin that begins over each eye, swings down into a semi-circle over the inner canthus and extends onto cheek"
  - nose blunted
  - depression b/w lower lip and chin
  - low set ears
- MSk abnormalities
  - bowed/clubbed legs w/ excessive flexion at hips and knees
  - sirenomelia: lower extremities completely fused
- dry skin
- pulmonary hypoplasia: due to lack of Proline (kidney is major source)
  - proline required for collagen formation in bronchiolar tree
- bell-shaped chest
- CVS, GI abnormalities

### **How can one diagnose BRA?**

- Px
  - characteristic Potter's facies
  - presence of oligohydramnios
  - anuria after 1st 24 hrs
  - respiratory distress in 1st 24 hrs
- Imaging
  - renal US: no kidneys
  - DMSA: lack of uptake

### **What is the treatment and prognosis of BRA?**

- termination of pregnancy
- 40% stillborn
  - most die in 24-48hrs: longest survivor was 39d

### **What is the incidence of unilateral renal agenesis (URA)?**

- 1 in 1100-1200
- M:F 1.8:1
- L > R

### **How can one classify URA?**

- classification based on timing of faulty differentiation: Magee (1979)
  - Type I: insult before 4th week
    - nondifferentiation of nephrogenic ridge
    - complete unilateral agenesis of GU structures → URA + unicornuate uterus
  - Type II: insult in early 4th week

## Chapter 55 Questions - Renal anomalies.doc

- maldeveloped mesonephric duct prevents crossover of Mullerian duct and fusion
- didelphys uterus + obstruction of ipsilateral horn and vagina
- Type III: insult after 4th week
- mesonephric and Mullerian ducts develop normally
- ureteral bud and metanephric blastema fail to form → absence of kidney only

### What are the anomalies associated w/ URA?

- GU
  - ipsilateral absence of ureter > 50%, rest often have partially developed ureter
  - anomalies of contralateral kidney: rare except for ectopia, malformation
  - anomalies of contralateral collecting system: UPJO (5%), UVJO (7%), VUR (30%)
  - ipsilateral adrenal agenesis: rare (<10%)
  - genital anomalies: more frequent
    - gonads usually intact
    - structures from mullerian/wolffian ducts often anomalous: vas, SV, ampulla, ED often absent (50%)
    - 80% of pts w/ CAVD have ipsilateral renal agenesis
    - unicornuate uterus, bicornuate uterus + didelphys, proximal vaginal atresia, absence of vagina
- CVS (30%)
  - cardiac defects
- GI (25%)
  - imperforate anus
  - anal/esophageal atresia
  - pharyngeal abnormalities
- MSK (14%)
  - vertebral anomalies

### What syndromes have been associated w/ URA?

- Turner's: 45XO
- Poland's
  - group of unilateral congenital abnormalities of chest wall +/- involvement of ipsilateral arm
  - commonest abnormality: absence of pectoralis major and minor
  - syndactyly w/ absence of sternal head of pectoralis major
- DiGeorge anomaly
  - member of a group of disorders that share in common a chromosome deletion, which results in monosomy 22q11 (CATCH-22 or DiGeorge/velocardiofacial [VCFS] syndrome)
  - thymus deficiency, conotruncal heart anomalies, dysmorphism, hypoparathyroidism, cleft palate
  - URA if associated w/ Type 1 DM in mother
- Kallman's
  - midline anomalies associated w/ anosmia
  - inability of hypothalamus to secrete GnRH
- VACTERL association: 20-30% have URA
  - vertebral, imperforate anus, cardiac, TE fistula, renal anomalies, limb anomalies

### How can one make the diagnosis of URA?

- no specific sx → suspect if:
  - unilateral absence of vas
  - unicornuate uterus
  - gas pattern on KUB shows colon in area of kidney
  - ipsilateral lying down adrenal
  - lack of kidney on US, DMSA
- contralateral kidney usually OK

### What is the management and prognosis of the child w/ URA?

- VCUG: high incidence of VUR
- advise against contact sports or strenuous exertion
- no evidence that pts w/ URA have increased susceptibility to other diseases
  - may have increased occurrence of htn, hyperuricemia, and decreased renal function

### What is the incidence of supernumerary kidney?

- very rare: 80 cases

## Chapter 55 Questions - Renal anomalies.doc

- M=F, L > R

### Describe the embryologic formation of a supernumerary kidney.

- 2nd ureteral outpouching off the Wolffian duct or branching from initial ureteral bud appears as a necessary 1st step
- nephrogenic anlage may divide into 2 metanephric tails

### What is the typical configuration of a supernumerary kidney?

- distinct parenchymatous mass that may be completely separate or only loosely attached to the major ipsilateral kidney
- 2 main kidneys usually normal, 3rd is small
- ipsilateral ureters may be bifid or completely duplicated
- variable ureteral relationships: common stem and single UO in 50%, 2 completely separate ureters in 50%
  - Weigert-Mayer principle usually observed (90%)
  - may have ectopic ureter opening into vagina or introitus

### What anomalies are associated w/ supernumerary kidneys?

- ipsilateral and contralateral kidneys usually normal
- no GU anomalies
- rarely any other anomalies

### What are the sx of a supernumerary kidney?

- rarely any sx: pain, fever, htn, mass → if infection or obstruction
  - UI if ureteral ectopia

### How can one classify renal ectopia?

- pelvic: opposite sacrum
- iliac (lumbar): rests near sacral promontory in iliac fossa, anterior to iliacs
- abdominal: above iliac crest adjacent to 2nd lumbar vertebrae
- thoracic: partial or complete protrusion of the kidney above the level of the diaphragm into the posterior mediastinum
- contralateral or crossed

### What is the incidence of renal ectopia?

- 1 in 500-1200
- M=F, L > R
- thoracic kidney: 140 cases, L > R 1.5:1, M:F 2:1

### Describe the embryologic formation of an ectopic kidney.

- ureteral bud arises from Wolffian duct at end of 4th week
- grows toward urogenital ridge and causes differentiation of metanephric blastema
  - during migration, bud matures into a normal collecting system and medial rotation of collecting system occurs
- prevention of normal movement of kidneys causes ectopia

### What factors may prevent the orderly movement of kidneys?

- ureteral bud maldevelopment
- defective metanephric blastema: fails to induce ascent
- genetic abnormalities
- maternal illnesses or teratogens
- vascular barrier

### What is the typical configuration of the ectopic kidney?

- usually smaller
- renal pelvis anterior: due to incomplete rotation
  - 56% have hydronephrosis, due to UPJO (35%), UVJO (15%), VUR (25%), or due to malrotation alone (25%)
- ureter usually enters bladder normally

### What anomalies are associated w/ ectopic kidneys?

- GU
  - contralateral kidneys usually normal
    - high incidence of contralateral agenesis
  - bilateral ectopia
  - hydronephrosis



## **Chapter 55 Questions - Renal anomalies.doc**

- genital anomalies: 15-45%
  - bicornuate or unicornuate uterus
  - rudimentary or absent uterus, vagina
  - vaginal duplication
  - UDT
  - urethral duplication
  - hypospadias
- adrenal agenesis
- skeletal anomalies
- cardiac anomalies

### **What are the sx of renal ectopia?**

- usually related to obstruction

### **What is the prognosis and management of the child w/ an ectopic kidney?**

- no more susceptible to disease than normal kidney
  - except for hydro or stones
  - malrotation may lead to impaired drainage of urine
- increased risk of trauma: not protected by ribs
- no increased risk of malignancy

### **What disorder leads to the development of cephalad renal ectopia?**

- omphalocele
  - liver herniates into omphalocele sac w/ intestines
  - kidneys continue to ascend until they are stopped by diaphragm

### **What factors may lead to the development of thoracic renal ectopia?**

- delayed closure of the diaphragm
  - allows for protracted renal ascent
- accelerated ascent from the kidney before normal diaphragmatic closure

### **What is the typical configuration of a thoracic kidney?**

- sits in posterior mediastinum, in foramen of Bochdalek
  - not within pleural space
- normal rotation
- may have adjacent hypoplastic lung

### **What anomalies are associated w/ thoracic kidneys?**

- elongated ureter
- adrenal in normal position
- slightly elevated hemidiaphragm
- no other consistent anomalies

### **What is the incidence of crossed renal ectopia +/- fusion?**

- 62 cases crossed ectopia without fusion
- M > F 2:1
- L→R ectopia 3X more common

### **What are the potential theories for the embryologic formation of a crossed fused kidney?**

- pressure from abnormally placed umbilical arteries
- ureteral bud wandering to opposite side: induces differentiation of contralateral nephrogenic anlage
- malalignment and abnormal rotation of caudal end of developing fetus
- teratogenic factors
- genetic influences

### **What is the typical configuration of the crossed fused kidney?**

- unilateral fused kidney w/ inferior ectopia: crossed kidney lies caudad to normal counterpart
  - most common
  - superior pole of ectopic kidney joins inferior aspect of normal kidney
  - 90% fused w/ mate

## Chapter 55 Questions - Renal anomalies.doc

- ureter from normal kidney enters bladder on same side, ureter from ectopic kidney crosses midline at pelvic brim, enters bladder on contralateral side
- both renal pelvis anterior
- solitary crossed ectopic kidney
  - kidney somewhat low
  - incompletely rotated
- sigmoid/S-shaped kidney: 2nd most common
  - ectopic kidney is inferior, but both renal pelvis is oriented correctly, and face in opposite directions
- lump/cake kidney
  - total kidney mass irregular and lobulated: extensive joining at lateral borders
  - both renal pelvis anteriorly facing
  - ureters do not cross
- L-shaped kidney
  - crossed kidney is transverse lying
- disc kidney
  - kidneys joined at medial borders
  - doughnut or ring shaped mass
  - pelvis somewhat anterior
- superior ectopic kidney
  - ectopic kidney lies superior to normal kidney
  - both pelvis lie anteriorly
- vasculature for all kidneys variable and unpredictable

### What anomalies are associated w/ crossed ectopic kidneys?

- GU
  - ureter not ectopic in 97%, normal trigone
  - VUR into ectopic kidney
  - cystic dysplasia
  - UPJO
  - carcinoma
  - **genital anomalies: 40%**
    - cryptorchidism
    - absence of vas
    - vaginal atresia
    - uterine anomaly
    - imperforate anus
- **skeletal anomalies: 50%**

### What are the sx of crossed ectopic kidneys?

- usually due to infection or obstruction
  - pain, pyuria, hematuria, UTI
- htn

### What is the most common renal fusion anomaly?

- horseshoe kidney

### What is the incidence of horseshoe kidney?

- 0.25% of pplx
- M:F 2:1

### What is the typical configuration of the horseshoe kidney?

- 2 distinct renal masses lying vertically on either side of the midline
- connected at their lower poles by parenchymatous or fibrous isthmus that crosses the midplane of the body
  - usually bulky isthmus, w/ own blood supply
  - located next to L3-4, anterior to aorta and IVC
- pelvis and ureters anteriorly placed
  - joining occurs prior to rotation of kidneys
  - calyces normal in number, but point posteriorly
    - lowermost calyces extend caudally and medially
  - ureter may insert high on renal pelvis and lie laterally

## Chapter 55 Questions - Renal anomalies.doc

- lower ureter is usually normal
- kidneys lie lower in abdomen than normal
  - IMA prevents full ascent
- variable blood supply

### What anomalies are associated w/ horseshoe kidney?

- skeletal anomalies
- CVS anomalies
  - VSD
- CNS anomalies
  - horseshoe in 3% of neural tube defects
- genetic anomalies
  - trisomy 18: 20%
  - Turner's syndrome: 60%
- GU anomalies
  - hypospadias: 4%
  - UDT: 4%
  - bicornuate uterus: 7%
  - septate vagina: 7%
  - ureteral duplication: 10%
  - ectopic ureterocele
  - VUR: 50%
  - cystic disease
  - Wilms': 2X incidence
  - TCC: due to urinary stasis

### What are the sx of horseshoe kidney?

- 1/3 asymptomatic
- sx usually related to stones, UTI, hydro
- UPJO in 1/3

### What findings on IVP are suggestive of horseshoe kidney?

- low lying kidneys, close to spine
- vertical/outward axis: lower pole of kidney closer to midline compared to upper
- continuation of lower pole of kidney toward/across midline
- orientation of collecting system: directly posterior to each pelvis
- high insertion of ureter

### What is the natural hx of horseshoe kidney?

- 60% sx-free
- RCC in 114 reported cases

### What is the incidence of rotation anomalies of the kidney?

- 1 in 400-1000
- frequent in Turner's
- M: F 2:1

### Describe the embryology of the malrotated kidney.

- medial rotation of collecting system occurs during 6<sup>th</sup> week, w/ renal migration
- rotation due to unequal branching of successive orders of budding ureteral tree
  - more parenchyma develops ventrally than dorsally

### What is the typical configuration of the malrotated kidney?

- ventral position: most common
  - pelvis is ventral, in same AP plane vs. calyces: no rotation
  - rarely: 360° turn
- ventromedial position
  - incompletely rotated kidney
- dorsal position: least common
  - kidney turns 180°, so pelvis is posterior to parenchyma, and vessels pass behind kidney

## Chapter 55 Questions - Renal anomalies.doc

- lateral position  
→ pelvis faces laterally, and parenchyma is medial

### What features are characteristic in the malrotated kidney?

- kidney shape: discoid, elongated, oval, triangular
- fetal lobulations always present
- dense fibrous tissue in hilum, distorting pelvis
- upper ureter courses laterally, and may be encased
- elongated pelvis, stretched calyces

### What is the incidence of aberrant/accessory/multiple renal vessels?

- 15-30% of kidneys have > 1 vessel
  - 1 early upper pole branch: 13%
  - 2 hilar arteries: 11%
  - 1 accessory upper pole branch: 6%
  - 1 accessory lower pole branch: 7%
  - 1 early lower pole branch: 3%
  - 3 hilar arteries: 2%
  - 2 hilar arteries, 1 w/ upper pole branch: 3%
- 70-85% of kidneys have 1 hilar artery

### Describe the embryology of multiple renal vessels.

- renal arterial tree is derived from 3 groups of primitive vascular channels
  - cranial group: 2 pairs of arteries dorsal to adrenal, form phrenic
  - middle group: 3 pairs of vessels that pass through adrenal area, form adrenal artery
  - caudal group: 4 pairs of arteries, become main renal artery
- by a process of elimination, 1 primitive renal pair becomes dominant vessel
  - polar arteries represent failure of complete degeneration of all primitive vascular channels

### What findings on IVP suggest an accessory pole artery?

- filling defect in renal pelvis c/w anomalous vasculature
- hydro + sharp cutoff in superior infundibulum
- UPJO + angulated ureter near pelvis + kidney w/ more vertical axis
- differences in timing and concentration of 1 renal segment or in entire kidney vs. other side

### What is the incidence of renal artery aneurysm?

- 0.1-0.3%

### How can one classify renal artery aneurysms?

- saccular: most common (93%)
  - localized outpouching that communicates w/ arterial lumen by narrow or wide opening
- fusiform
  - aneurysm located at bifurcation of main renal artery and its anterior and posterior division or at one of the more distal branches
- dissecting
- AV

### What d/o are associated w/ RAA?

- ADPKD

### What are the sx of renal artery aneurysms?

- Sx
  - most are silent
    - esp in children (48%)
  - pain: 15%
  - hematuria: 30%
  - htn: 55% → due to compression of adjacent parenchyma or to altered blood flow
- Signs
  - pulsatile mass in region of renal hilum
  - bruit on abdo auscultation

## Chapter 55 Questions - Renal anomalies.doc

### What are the indications for surgical tx of a renal artery aneurysm?

- uncontrollable htn
- incomplete ringlike calcification
- > 2.5cm
- female pt, likely to get pregnant
- increasing in size
- AV fistula present
  - spontaneous rupture: 10%

### How can one classify renal AV fistulae?

- congenital: <25%
  - cirroid configuration, multiple communications b/w main or segmental renal arteries and venous channels
  - rarely present before age 20-30
  - F:M 3:1, R>L
  - usually located in upper pole: 45%
- acquired: >75%
  - trauma, inflammation, renal surgery, perc renal bx

### What are the sx of renal AV fistula?

- bruit: 75%
- htn: 40-50%
  - decreased perfusion of renal parenchyma distal to fistulous site: RAA mediated htn
- increased venous return, high CO
  - leads to LVH, high-output cardiac failure
- hematuria: >75%
- pain
- mass: 10%

### What are the radiologic signs of renal AV fistula?

- IVP
  - decreased or absent function in 1 segment or entire portion of involved kidney
  - filling defect in renal pelvis or calyces
  - calyceal distortion/obstruction distal to site of lesion
- angio
  - cirroid appearance w/ multiple small tortuous channels, prompt venous filling
  - enlarged renal and gonadal vein

### What is the tx for AV fistula?

- nephrectomy or partial
- vascular ligation
- selective embolization
- balloon catheter occlusion

### What is a calyceal diverticulum?

- cystic cavity lined by transitional epithelium
- encased within renal substance, situated peripheral to minor calyx, to which it is connected by a narrow channel

### What is the incidence of calyceal diverticulum?

- 4.5 per 1000

### How can one classify calyceal diverticulae?

- Type I: occur adjacent to upper- or occasionally a lower-pole calyx
- Type II: larger, communicate directly w/ renal pelvis

### What are the theories that have been used to explain the formation of calyceal diverticulae?

- persistence of isolated branches of the ureter
- localized cortical abscess draining into a calyx
- obstruction due to stone formation
- progressive fibrosis of an infundibular stenosis

## **Chapter 55 Questions - Renal anomalies.doc**

- renal injury
- achalasia
- spasm or dysfunction of one of the supposed sphincters surrounding a minor calyx

### **What are the complications of calyceal diverticulae (and the indications for surgery)?**

- infection
- milk of calcium
- stone formation
- hematuria
- pain

### **What is hydrocalycosis?**

- rare cystic dilation of a major calyx w/ demonstrable connection to the renal pelvis
- lined by transitional epithelium

### **What are the causes of hydrocalycosis?**

- congenital or acquired intrinsic obstruction → ex: parapelvic cyst
- obstruction of upper infundibulum by vessels, stenosis
- achalasia of ring of muscle at entrance to infundibulum

### **What are the sx of hydrocalycosis?**

- pain, mass, hematuria, infection

### **What is the DDx of hydrocalycosis?**

- ureteral obstruction
- recurrent pyelo + calyceal clubbing
- medullary necrosis
- renal TB
- large calyceal diverticulum
- megacalycosis

### **What is the treatment of hydrocalycosis?**

- dimembered infundibulopyelostomy
- percutaneous dilation

### **What is megacalycosis?**

- congenital nonobstructive enlargement of calyces resulting from malformation of the renal papillae  
→ X-linked partially recessive gene w/ reduced penetrance in females
- calyces dilated, malformed, may be increased in number
- UPJ normally funneled, no obstruction
- normal cortical tissue
- underdeveloped medulla
- short collecting tubules
- mild d/o of maximal concentrating ability

### **Describe the epidemiology of megacalycosis.**

- M:F 6:1
- only in whites
- bilateral almost all in M, segmental unilateral involvement only in F

### **What is a unipapillary kidney?**

- rare anomaly: due to failure of progressive branching after the 1<sup>st</sup> 3-5 generations of ureter
- solitary calyx drains a ridgelike papilla

### **What are the histologic abnormalities seen w/ unipapillary kidneys?**

- glomerulosclerosis
- tubular atrophy
- increased fibrosis
- smaller kidneys
- reduced function

## **Chapter 55 Questions - Renal anomalies.doc**

### **What anomalies are associated w/ unipapillary kidneys?**

- contralateral renal agenesis
- genital abnormalities
- abnormalities of proximal ureter
  - megaureter, VUR, ectopic ureter

### **What are extrarenal calyces?**

- congenital: major calyces and renal pelvis are outside the parenchyma of the kidney
  - discoid kidney
- anomalous renal vessels
- due to abnormal nephrogenic anlage, or too early and rapidly developing ureteral bud
- usually no sx: may have stasis, infection, stones

### **What is a pseudotumour of the kidney?**

- localized mass b/w infundibula of the upper and middle calyceal groups
  - called hypertrophied column of Bertin
- may compress and deform the adjacent pelvis and calyces
- normal function

### **What is infundibulopelvic dysgenesis?**

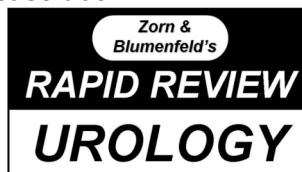
- link b/w cystic dysplasia of the kidney and gross hydronephrosis
- dysmorphic kidney w/ varying degrees of infundibular or infundibulopelvis stenosis
- due to extensive dysgenesis of the pyelocalyceal system w/ preservation of renal function
- usually bilateral, associated w/ VUR
- sx: UTI, htn, pain
- renal deterioration is common, eventually leading to ESRD in all pts → due to hyperfiltration injury

### **What percentage of renal pelvises are bifid?**

- 10%







## **Chapter 56**

### **• Renal Dysgenesis and Cystic Disease of the Kidney •**

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#### **What is the protein product of the PKD gene?**

- polycystin-1: long chain glycoprotein produced by ADPKD gene PKD1 on chromosome 16
- polycystin-2: produced by PKD2 gene on chromosome 4
  - play a role in normal tubulogenesis in the developing metanephros

#### **What is the "two-hit" theory?**

- Knudson's (1991) 2-hit hypothesis
  - 1<sup>st</sup> hit in inherited mutation is found in all cells of an individual: germ-line mutation
  - 2<sup>nd</sup> hit occurs when wild-type allele spontaneously mutates within a specific organ
- VHL wild-type gene prone to spontaneous mutation
  - propensity to form clear cell RCC

#### **What is the role of WT1 in the development of tumours?**

- WT1 (Wilms' tumour) gene is a protooncogene on chromosome 11
  - IGF-2 normally present at high levels in developing metanephric blastema, and inhibits mesenchymal cell apoptosis
  - WT1 suppresses IGF-2 activity, allowing development of ureteric bud
  - if WT1 is defective, IGF-2 is not suppressed, and blastemal cell proliferate

#### **What are the genetic steps involved in renal development?**

- GDNF precedes the branching process
  - signalling agent produced by mesenchymal cells
- tyrosine kinase c-ret: receptor for GDNF
  - located on Wolffian duct, on tip of ureteric bud, and in branching ureteric tips
  - GDNF binds to c-ret, signalling ureteric bud formation and branching
  - activates WNT11, inducing ureteric branching
- pPAX2: induces mesenchymal cells to change into epithelial cells
  - epithelial cells eventually form single simple tubules and future nephrons
- pWNT4: involved in development of CAMs, orienting cells to adhere to form tubule
  - $\beta$ -catenin: CAM that binds epithelial cells in a way to form tubules

#### **How does $\beta$ -catenin play a role in renal development?**

- is a CAM that allows for proper epithelial cell orientation and tubule formation
- GSK-3 (glycogen synthetase kinase-3) inhibits the  $\beta$ -catenin molecule when attached to it
- APC (adenomatous polyposis coli) can also destabilize  $\beta$ -catenin
- pVHL (normal product of VHL gene) destabilizes  $\beta$ -catenin by enhancing APC and GSK-3 binding
  - pWNT4 blocks the destabilizing effect of GSK-3, which increases the levels of  $\beta$ -catenin
  - polycystin activates pWNT4

#### **What is renal-colomba syndrome?**

- heterogeneous PAX2 mutation
  - blindness due to optic nerve malformation = colomba
  - unilateral hypoplastic kidney
  - VUR

#### **What is Mayer-Rokitansky-Kuster-Hauser syndrome?**

- unilateral renal agenesis or renal ectopia
- ipsilateral Mullerian defects
- vaginal agenesis

#### **What is meant by renal dysgenesis?**

## Chapter 56 Questions - Renal Cystic Disease.doc

- maldevelopment of the kidney that affects its size, shape, or structure
- 3 types:
  - dysplastic
    - contains focal, diffuse, or segmentally arranged primitive structures (primitive ducts and cartilage) due to abnormal differentiation
    - cysts present = cystic dysplasia
    - entire kidney is dysplastic with ++ cysts = MCDK
  - hypoplastic
  - cystic

### What is the etiology of renal dysplasia?

- unclear
- Mackie and Stephens (1975) bud theory
  - abnormal ureteric budding can lead not only to ectopic orifice but also inappropriate penetration of the blastema, causing renal dysplasia
  - high correlation b/w degree of lateral ectopia of orifice and extent of dysplasia for lower pole moiety
- obstruction: significant factor in dysplasia
  - if both kidneys drain poorly, both kidneys may be dysplastic

### What are the histologic signs of dysplasia?

- primitive ducts: lined by cuboidal or tall columnar epithelium (+/- ciliation)
  - surrounded by concentric rings of connective tissue containing collagen and few smooth muscle cells but no elastin
  - more severely deformed the kidney, the more extensive the primitive ducts
- primitive ductules: smaller than primitive ducts, no smooth muscle
- primitive tubules and glomeruli
- cysts and loose disorganized mesenchyme and fibrous tissue

### What is familial renal adysplasia?

- all or part of the following group of anomalies that appear in a single family
  - renal agenesis
  - renal dysplasia
  - MCDK
  - renal aplasia
- AD transmission
  - ureteric bud anomaly or defect of the metanephric blastema

### How can one classify hypoplasia and hypodysplasia?

- Hypoplasia: less than N # of calyces and nephrons, and are not dysplastic or embryonic
  - true (oligonephronia) +/- abnormal UO
  - oligomeganephronia = marked reduction in # of nephrons, w/ hypertrophy of each nephron
    - usually bilateral, sporadic malformation
  - segmental (Ask-Upmark kidney)
    - due to chronic pyelo from VUR
- Hypodysplasia
  - w/ N UO
    - w/ obstruction: primary obstructive megaureter, UPJO
    - w/o obstruction: "dwarf" kidney, due to deficient metanephric blastema
  - w/ abnormal UO: usually thin w/ rounded ectatic calyces, due to insufficient divisions of the ureteral bud
    - lateral ectopia: usually has VUR → high pressure from constant VUR causes premature termination of calyceal division
    - medial or caudal ectopia w/ ureterocele: usually obstructed w/ hydro of severely dysplastic
  - w/ urethral obstruction (PUV) → 2 types:
    - less severe: small subcapsular cysts w/ normal renal fn
    - more severe: large cysts w/ numerous islands of cartilage → more severe obstruction and VUR, earlier onset
      - ◆ position of UO correlates well w/ extent of dysplasia
  - Prune-Belly syndrome
    - grossly deformed kidneys, wide tortuous ureters, large laterally placed orifices

### What are the clinical features of oligonephronia?

- may be severe or absent

## Chapter 56 Questions - Renal Cystic Disease.doc

- renal insufficiency, dehydration, FTT, resp problems
- proven w/ renal bx

### What are the clinical features of oligomeganephronia?

- M > F
- associated w/ low birth weight
- vomiting, dehydration, thirst, polyuria
- proteinuria
- decreased renal function
- severe growth retardation
- ocular, auditory, and skeletal anomalies
- mental retardation

### What is the histopathology seen w/ oligomeganephronia?

- small kidneys
- decreased # nephrons w/ increased size
- reduced # of renal segments
- enlarged glomeruli, JGA
- interstitial fibrosis and atrophy w/ hyalinization of glomeruli

### What is the tx for oligomeganephronia?

- high fluid intake and correction of salt loss and acidosis
- limit protein intake
- HD
- renal transplantation

### What are the features of the Ask-Upmark kidney?

- distinctive small kidneys, may be due to VUR and pyelo → etiology unknown
- Clinical
  - pts > 10 yrs
  - F:M 2:1
  - severe htn, headache, retinopathy
  - proteinuria, renal insufficiency
- Histologic
  - kidney smaller than normal
  - deep grooves on lateral convexity
  - parenchyma made of tubules that resemble thyroid
  - arteriosclerosis, JGA hyperplasia

### What is the treatment for the Ask-Upmark kidney?

- unilateral: partial or total nephrectomy
- bilateral: medical management of renal insufficiency, HD, transplant

### How can one classify renal cystic disease?

- Genetic
  - ARPKD: chromosome 6
  - ADPKD
    - PKD1: chromosome 16
    - PKD2: chromosome 4
  - juvenile nephronophthisis-medullary cystic disease complex: chromosome 2
  - AR juvenile nephronophthisis
  - AD medullary cystic disease
  - congenital nephrosis (familial nephrotic syndrome): chromosome 19
  - familial hypoplastic glomerulocystic disease
  - multiple malformation syndromes w/ renal cysts: TS, VHL
- Non-genetic
  - MCDK
  - benign multilocular cysts (cystic nephroma)
  - simple cyst
  - medullary sponge kidney (MSK)

## Chapter 56 Questions - Renal Cystic Disease.doc

- sporadic glomerulocystic kidney disease
- ARCD
- calyceal diverticulum

### What is the difference b/w renal cysts or ectatic tubules?

- ducts dilated to 4X normal diameter = cyst

### In which cystic disorders do the cysts have a hyperplastic lining?

- ADPKD
- TS
- VHL
- ARCD

### What is the difference b/w the terms multicystic and polycystic?

- multicystic = dysplastic entity (MCDK)
- polycystic = many separate entities, all w/o dysplasia (ADPKD, ARPKD, TS, VHL)

### What are the genetics of ARPKD?

- rare disease: 1 in 40000
- 50% of affected newborns die, 50% of survivors die by 10 yrs
- AR trait, single gene on chromosome 6

### What are the features of ARPKD?

- Clinical → 4 subtypes:
  - Perinatal
    - present at birth w/ huge abdominal masses (nonbosselated kidneys – covered in knobs) that are hard, do not transilluminate, may be large enough to impede delivery
    - normal liver w/ minimal periportal fibrosis
    - oligohydramnios, Potter's facies, respiratory distress, oliguria
    - usually die within 2 mo from respiratory or renal failure
  - Neonatal
    - present within 1 mo w/ large kidneys, hepatic enlargement
    - mild hepatic fibrosis
    - eventually get renal failure
  - Infantile
    - present aged 3-6mo w/ large kidneys, hepatosplenomegaly
    - develop CRF, portal hypertension
    - moderate periportal fibrosis
  - Juvenile
    - present age 1-5 yrs, w/ portal hypertension, esophageal varices, hepatosplenomegaly
    - minimal renal involvement
- Histologic
  - kidneys retain fetal lobulation
  - cortex crowded w/ minute cysts
  - cysts derived principally from collecting ducts
  - normal renal pedicle and ureter
  - periportal fibrosis

### How does one evaluate and manage the child w/ ARPKD?

- US abdomen
  - enlarged homogenous hyperechoic kidneys: due to large # of interfaces from dilated collecting ducts
  - smooth
  - symmetric
  - echogenic
  - cysts elsewhere
  - echogenic kidneys
- IVP
  - functioning kidneys w/ characteristic radial or medullary streaking (**sunburst pattern**) caused by dilated collecting tubules filled w/ contrast
- family hx

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- at least 3 generations
- genetic counselling
- treat htn, CHF, renal and hepatic failure
  - splenorenal shunt
  - gastric section and reanastomosis for esophageal varices
  - hemodialysis and renal transplant

### What is the DDX of a newborn w/ bilateral large cystic kidneys?

- No macrocysts, homogenous, hyperechogenic kidneys
  - ARPKD
  - ADPKD
  - sporadic glomerulocystic kidney disease
  - contrast nephropathy
  - RVT
- Macrocysts present
  - ARPKD
  - ADPKD
  - sporadic glomerulocystic kidney disease
  - TS

### What anomalies are associated w/ ADPKD?

- cysts of liver, pancreas, lungs, spleen
- berry aneurysms
- colonic diverticulae
- mitral valve prolapse

### What are the genetics of ADPKD?

- 3 genes
  - PKD1: chromosome 16 short arm (85-90%)
  - PKD2: chromosome 4 (5-10%)
    - usually have later onset of sx, slower progression of disease
  - PKD3: not identified (small %)
- 100% penetrance
- AD
- 96% clinically manifest the disease by age 90
- genetic imprinting: disease is more severe if manifests earlier when inherited from mother vs. father

### What theories describe the potential causes of ADPKD?

- **epithelial hyperplasia → major component of cyst development**
  - may cause tubular obstruction, causing BM weakening and secondary proximal outpouching
- defect in BM of tubules, causing cyst development
  - leads to increased compliance, allowing outpockets to develop
- defect in proteins of the supportive ECM
- location of Na-K-ATPase in cystic epithelium
  - located in apical position, rather than normally in basolateral position
  - causes fluid to enter cyst lumen rather than leave it

### What are the features of ADPKD?

- Clinical
  - sx usually present b/w age 30-50
  - hypertension: principal form of presentation
    - due to stretching of renal vessels around cysts, causing distal ischemia and RAAS activation
  - hematuria
    - micro/gross hematuria in 50%
    - presenting sx in 20-35%
  - flank pain, GI sx (due to colonic diverticula)
  - renal colic from clots or stone: 20-30%
  - renomegaly, proteinuria
  - hepatic cysts
    - more likely in adults, F > M

## Chapter 56 Questions - Renal Cystic Disease.doc

- often grow, but rarely cause any important effects: portal htn, bleeding esophageal varices
- congenital hepatic fibrosis may occur
- berry aneurysms: 10-40%
  - 9% pts die from IC bleed (SAH)
- MVP
- colonic diverticulae
- respiratory distress at birth if severe
- Histologic
  - renal cysts from few mm to cm in diameter
  - appear diffusely throughout cortex and medulla
    - variant form: renal cysts located primarily in Bowman's space
      - ◆ absence of family members
  - epithelial lining resembles segment of nephron from which the cyst is derived
  - epithelial hyperplasia or adenoma formation
    - hyperplastic polyps in 91%
  - thickened BM
  - arteriosclerosis
  - apoptosis: in lining of cysts
  - focal tubular dilation

### What is the association b/w ADPKD and RCC?

- incidence of RCC in ADPKD is no higher than general population
  - incidence of renal adenomas is almost as high in ADPKD as in ARCD (20%)
- RCC in ADPKD is more often bilateral (12% vs. 1%), multicentric (28% vs. 6%) and sarcomatoid (33% vs. 1%)

### What is involved in the evaluation and management of ADPKD?

- Hx
  - FHx spanning 3 generations: renal disease, htn, strokes
  - dx ADPKD if renal cysts + 2 of:
    - bilateral renal enlargement
    - 3 or more hepatic cysts
    - cerebral artery aneurysm
    - solitary cyst of arachnoid, pineal gland, pancreas, or spleen
- Imaging
  - US
    - 50% of affected kidneys are large w/ identifiable macrocysts
    - may appear identical to ARPKD, w/o macrocysts
  - IVP
    - calyces stretched by cysts
    - may simulate ARPKD w/ medullary streaking
    - bilateral renal enlargement, calyceal distortion, Swiss cheese appearance
  - CT: hemorrhage: 50-90 HU
  - MR: no contrast needed
- Screening of family
  - pts children examined by US
    - 83% of pts +ve for PKD1 defect have cysts by age 30, 100% after age 30
    - w/ +ve FHx, pts < 30 need 2 cysts for +ve dx, pts > 30 need 2 cysts in each kidney for +ve dx, pts > 60 need > 4 cysts in each kidney for +ve dx
- Treatment
  - control of hypertension and renal insufficiency
    - M > F
    - rate of renal deterioration correlates w/ cyst growth: cysts cause pressure atrophy
    - HD, transplant
  - control of pain from stones, clots, hemorrhage into a cyst
    - Rovsing's operation: unroofing of cysts → may help w/ pain control
  - treatment of cyst infections
    - need lipid soluble antibiotics: TMP/SMX, chloramphenicol, quinolones
- Prevention
  - BP monitoring and tests of renal fn
    - ESRD in 2% by age 40, 23% by age 50, 48% by age 73

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- control infections and htn
- offer advice on marriage and kids

### What is juvenile nephronophthisis-medullary cystic disease complex?

- 2 cystic conditions similar anatomically and clinically
- different modes of transmission and different clinical onset

### Describe the genetics of juvenile nephronophthisis-medullary cystic disease complex.

- JN: AR trait, manifests b/w age 6 and 20 → 1 in 50,000
  - ESRD by age 13, always before age 25
  - gene defect on chromosome 2
- MCD: AD trait, manifests in early adulthood, in all by age 50 → 1 in 100,000
  - ESRD by age 20-30
  - unknown gene defect

### What are the features of JN-MCDC?

- Clinical
  - JN
    - polyuria and polydipsia in > 80%
      - ◆ polyuria due to severe renal tubular defect associated w/ inability to conserve Na
      - ◆ polyuria resistant to vasopressin: requires large Na defect
    - salt-losing nephropathy: present in JN, not in MCDC
    - retinal disorders
      - ◆ retinitis pigmentosa + JN = Senior-Løken syndrome (renal-retinal syndrome)
    - blindness, obesity, DM, nerve deafness = Alstrom's syndrome
    - extrarenal abnormalities
  - MCDC
    - polyuria and polydipsia in 80%
    - hypertension: present in MCDC, not in JN
    - growth slows, ESRD
- Histologic
  - interstitial nephritis: round cell infiltrates, tubular dilation w/ atrophy
  - atrophy begins in cortex, later involves entire kidney: becomes small
  - cysts from 1-10mm: in 85% of MCDC, 40% of JN
    - present at corticomedullary junction
    - cysts appear after renal failure w/ JN, before renal failure w/ MCDC
  - alternating areas of thickening and thinning BM
    - more common in JN

### What is involved in the evaluation and management of the pt w/ JN-MCDC?

- Imaging
  - IVP
    - normal or small kidney
    - homogenous streaking of medulla: retention of contrast in tubules
  - US
    - cysts rarely visible early in disease
- Treatment
  - Na replacement
  - HD, transplant

### What are the two types of congenital nephrosis?

- Finnish type (CNF): more common, AR
- diffuse mesangial sclerosis (DMS)
  - is the same nephropathy present in Denys-Drash syndrome (Wilms', male pseudohermaphroditism, + nephropathy)
  - treat both w/ transplant

### What are the features of congenital nephrosis?

- Clinical
  - CNF

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- enlarged and edematous placenta: > 25% of birth weight
- proteinuria in 1<sup>st</sup> urinalysis
- edema by 3mo
- ½ pts die w/o HD by age 6mo
- DMS
  - placenta normal weight
  - onset of sx variable: dx usually by age 1 yr
  - all have ESRD by age 3 yrs
- Histologic
  - normal sized kidneys
  - proximal tubular dilation
  - fusion of glomerular podocytes
  - interstitial fibrosis
  - DMS
    - accumulation of PAS-+ve and silver phosphate staining mesangial fibrils
    - sclerosis of glomeruli
  - CNF
    - proliferation of glomerular mesangial cells

### What are the features of familial hypoplastic glomerulocystic kidney disease?

- chronic renal failure
- small/normal kidneys w/ irregular calyceal outlines and abnormal papillae
- present in 2 generations
- glomerular cysts
  - thin walled, subcapsular
  - may have tubular atrophy w/ normal glomeruli and tubules in deeper cortex

### What is the classic triad of TS?

- epilepsy: 80%
- mental retardation: 60%
- adenoma sebaceum: 75%
  - flesh-coloured papules of angiofibroma, present in malar area
  - earlier skin lesion: "ash leaf" papule
- hallmark lesion: superficial cortical hamartoma of cerebrum

### Describe the genetics of TS.

- AD trait in 25-40%
  - TSC1: chromosome 9
  - TSC2: chromosome 16
- if severe polycystic kidneys in pt w/ TS, likely represents contiguous gene syndrome
  - defects in both TSC2 and PKD1

### What are the features of TS?

- Clinical
  - epilepsy, MR, adenoma sebaceum
  - renal cysts: in 20% before 3yrs
    - abdominal mass and distended abdomen
  - AML: in 40-80%
    - embolize or excise if > 4cm
  - renal failure: uncommon before age 30
  - RCC: up to 2%
    - VHL, ARCD > TS > ADPKD
- Histologic
  - unique renal cysts: lining of hyperplastic, hypertrophic eosinophilic cells
  - large hyperchromatic nuclei, few mitoses
  - cells aggregate into tumourlets

### What is involved in the evaluation of the pt w/ TS?

- full investigation of pts w/ seizure d/o, hypomelanotic macules, and pts w/ cysts
- MR



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- multiple calcified subepididymal nodules penetrating into ventricle
- US
  - renal cysts and AMLs

### Describe the genetics of VHL.

- gene associated w/ transmission of VHL is on chromosome 3 (3p24-25)
- penetrance 100%
- AR tumour suppressor gene
- many different mutations of VHL gene
  - Type 1: RCC w/o pheo
  - Type 2: RCC w/ pheo
  - Type 3: pheo w/o RCC
- M = F

### What are the features of VHL?

- Clinical
  - present at age 35-40
  - renal cysts: in 76%, bilateral in 75%, multifocal in 87%
    - cause pain, mass, hematuria
  - RCC: in 35-38% → dx at age 30-40
    - **30% of VHL pts die from RCC**
    - **VHL, ARCD > TS > ADPKD**
  - pheo: in 10-17%
  - cerebellar hemangioma: sx by age 15-40
  - retinal angioma
    - bleeding → blurred vision, retinal detachment, blindness
    - treat w/ laser therapy
  - pancreatic cysts
  - epididymal cyst/cystadenoma
- Histologic
  - renal cysts and tumours: multiple and bilateral
    - simple benign cysts w/ flattened epithelium
    - cysts > 2cm more likely to have RCC components
  - spectrum of pathology
    - simple cyst → proliferative cyst → complex neoplastic projections into cyst lumen → adenoma → RCC

### What is involved in the evaluation of the pt w/ VHL?

- US: absence of internal echoes, well-defined margins, acoustic enhancement
- CT: difficult to distinguish lesions from cysts
  - if RCC suspected, get renal angio w/ magnification and subtraction
- Screening
  - genetically affected members require screening for tumour
  - abdo CT if asymptomatically genetically affected related b/w ages of 18-20
    - if no disease found, repeat q4yr

### What is the tx for the pt w/ VHL?

- small low-grade tumours: excision/partial if < 5cm, nephrectomy if > 5cm
  - renal-sparing surgery: 75% recurrence in contralateral kidney
- low-grade bilateral tumours: treat cautiously like unilateral tumours w/ close monitoring
- bilateral high-grade tumours: bilateral nephrectomy

### What is MCDK?

- severe form of non-genetic cystic dysplastic kidney
  - males: more likely to have unilateral MCDK
  - females: more likely to have bilateral MCDK → incompatible w/ survival
  - L > R
- if cysts are small → called solid cystic dysplasia
- if identifiable renal pelvis → called hydronephrotic form of multicystic kidney
  - connections exist b/w cysts

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What theories have been created to explain the etiology of MCDK?

- extreme form of hydro due to atresia of ureter or renal pelvis
- failure of the union b/w ureteric bud and metanephric blastema
  - leads to cystic dilation

### What are the features of MCDK?

- Clinical
  - abdo pain
  - hematuria
  - htn
- Histologic
  - non-reniform kidney
    - "bunch of grapes"
  - no calyceal drainage system
  - ureter partly or totally atretic
  - renal size highly variable
    - MCDK w/ large cysts tend to be large w/ little stroma
    - MCDK w/ small cysts are smaller and more solid
  - variable blood supply
  - cysts lined by low cuboidal epithelium
    - separated by thin septa of fibrous tissue and primitive dysplastic elements
  - immature glomeruli seen, occasional mature glomeruli

### What anomalies are associated w/ MCDK?

- GU
  - contralateral UPJO: 3-12%
  - contralateral VUR: 18-43% → get VCUG
  - involution of MCDK → "renal aplasia", or "aplastic dysplasia", or "nubbin"
  - cystic dysplasia of the testes
    - benign rare lesion of the testes: more often seen w/ renal agenesis than w/ MCDK

### How can one distinguish b/w UPJO and MCDK?

- MCDK
  - haphazard distribution of cysts of various sizes w/o larger central or medial cyst
  - no visible communications b/w cysts
  - very small cysts appear b/w the cysts
  - no function on DMSA
  - angio shows absent or small renal artery
  - cysto: hemitrigone and absent UO on affected side
  - VCUG: contralateral VUR
- UPJO
  - cysts or calyces organized around the periphery of the kidney
  - communication seen b/w cysts
  - absence of small cysts b/w cysts
  - function seen on DMSA

### How does one treat the child w/ MCDK?

- identify abnormalities of the contralateral kidney
- follow for RCC
  - risk 4X greater in child w/ MCDK than in general pplx
  - no need for prophylactic nephrectomy
  - RBUS q3mo until 8 yrs of age: risk very small thereafter
- BP monitoring, treat htn if present
  - occurs infrequently w/ MCDK
  - may resolve w/ nephrectomy

### What is the Ddx for a multilocular cystic lesion in children and in adults?

- Pediatric
  - benign multilocular cyst
  - multilocular cystic partially differentiated Wilms' tumour

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- multilocular cyst w/ nodules of Wilms'
- cystic Wilms'
- Adult
  - benign multilocular cyst
  - multilocular cystic RCC
  - ?multilocular cyst w/ nodules of RCC
  - cystic RCC

### What are the features of benign multilocular cysts (cystic nephroma)?

- Clinical
  - present before age 4 or after age 30
    - 2X likely to be M if < 4
    - 8X likely to be F if > 30
  - children: asymptomatic flank mass is most common finding
  - adults: symptomatic flank mass, abdo pain, hematuria
    - bleeding due to herniation of cyst through transitional epithelium into the renal pelvis
- Histologic
  - bulky lesions circumscribed by thick capsule
    - compression of adjacent renal parenchyma
  - lesion may extend into perinephric space
  - loculi do not communicate
  - contains straw coloured clear fluid
  - lined by cuboidal or low columnar epithelial cells
    - cystic Wilms' tumour: cysts lined by epithelial cells
  - hobnail appearance: eosinophilic cuboidal cells may project into the cyst lumen
  - interlocular septa contain tissue of 2 different types:
    - fibrous tissue only: in adults or children
    - embryonic-type tissue: in children only
  - poorly differentiated tissue (tubules, glomeruli, mesenchyme, skeletal muscle, cartilage) not seen in benign cysts

### What is Perlmann's tumour?

- benign multilocular cystic lesion in adults

What is the treatment for benign multilocular cyst?

- nephrectomy: US and CT not able to distinguish from malignant lesion
  - multilocular cyst w/ nodules of Wilms' or cystic Wilms': treat as per Wilms' → favourable outlook

### Describe the incidence of simple cysts.

- present in 0.1% at birth, 20% by age 40, 33% after age 60
- M > F

### What are the features of simple cysts in children?

- Clinical
  - abdo mass, pain, hematuria, htn
  - calyceal or renal pelvis obstruction
  - may rupture into collecting system: become pseudocalyceal diverticulum
- Histologic
  - oval to round, 0-10cm
    - most < 2cm diameter
  - smooth outline bordered by single layer of flattened cuboidal epithelium
  - wall is fibrous, varying thickness
  - filled w/ transudate-like clear or straw coloured fluid

### How can one distinguish b/w ruptured cyst and calyceal diverticulum?

- diverticuli should have linings of transitional epithelium
- simple cysts should have lining of single layer of flattened or cuboidal epithelium

What are the criteria of a simple cyst on US?

- absence of internal echoes
- thin walled w/ smooth margin

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- good transmission of sound waves w/ acoustic enhancement
- spherical/ovoid shape

### What are the criteria for simple cyst on CT?

- smooth walls
- spherical/ovoid shape
- homogenous content
  - density from -10 to +20 HU: similar to water
  - if hyperdense cyst (20-90 HU) likely to be simple cyst if no enhancement after IV contrast, < 3cm, and ¼ of cyst extrarenal
- no enhancement after IV contrast
  - cysts have no blood vessels: if enhances, implies vascular tissue
  - watch for de-enhancement if no pre-contrast film obtained

### What are the DDX of a cyst?

- complicated cyst: filled w/ blood, pus, calcification
- cystic neoplasms

### What are the indications for cyst puncture?

- suspected infection
- low-level echoes on US but classic cyst on CT
- borderline lesion on poor surgical candidate

### What is the appearance of an infected cyst on imaging?

- thickened calcified wall
  - 1-3% calcified due to hemorrhage, infection, or ischemia
  - 6% of simple cysts can hemorrhage
- presence of debris
- MR: bright T2-weighted imaging if hemorrhage

### What variations of simple cysts exist?

- Unilateral renal cystic disease
  - rare: large renal cysts of varying size appearing side by side, more numerous at one pole
  - requires long-term follow-up demonstrating absence of cyst development in contralateral kidney, no FHx cystic disease
  - consider genetic studies to r/o TS and VHL
- AD simple cyst disease
  - may not exist yet

### What is the treatment of simple cysts?

- pyelocalyceal obstruction or htn: unroofing the cyst or sclerotherapy
- pain: sclerosis of cyst w/ bismuth phosphate, perc resection, marsupialization

### What is the Bosniak classification of simple and complex cysts?

- Bosniak I: simple benign cyst: through transmission, no echoes, smooth walled → no surgery
- Bosniak II: minimal septation, minimal calcification, high density → no surgery
  - IIF: not well defined by Bosniak → minimally complicated class II lesion that requires follow-up
- Bosniak III: more complicated, cannot be distinguished from malignancy, more calcification, thicker septations → OR
- Bosniak IV: large cystic malignant lesion, irregular margins, solid vascular elements → OR

### What are the features of medullary sponge kidney?

- Clinical
  - presentation after age 20
  - most common presentations:
    - renal colic: most common (50-60%)
    - UTI: 20-33%
    - gross hematuria: 10-18%
  - stones: 2-26%
    - Ca oxalate +/- Ca phosphate
  - hypercalcemia: 1/3 to 1/2

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- Histologic
  - dilated intrapapillary collecting ducts and small medullary cysts
  - cysts lined by collecting duct epithelium and communicated w/ collecting tubules
  - cysts may have concretions made of apatite +/- Ca
  - bilateral in 75%

### What anomalies are associated w/ MSK?

- small # of isolated AD and AR inheritance
- hemihypertrophy, BWS, Ehler-Danlos, anodontia, Karoli's disease (hepatic and pancreatic cystic disease in ARPKD)

### How can one diagnose MSK?

- IVP: more sensitive than CT
  - enlarged kidneys +/- calcification
  - elongated papillary tubules or cavities that fill w/ contrast
    - may resemble bunches of grapes or bouquets of flowers, or discrete linear stripes
  - papillary contrast blush and persistent medullary opacification
- US
  - not helpful, as cysts are small

### What is involved in the treatment of MSK?

- thiazides
  - lower hypercalciuria and limit stone formation
  - use in pts w/ stones even if hypercalciuria not present
- inorganic phosphates
  - useful if thiazides cannot be used
  - do not use in pts w/ UTIs from urease producing organisms → cause struvite stones
- frequent urine cultures
- lithotripsy and PCNL for stones

### What conditions are associated w/ glomerular cysts?

- sporadic glomerulocystic kidney disease
- familial hypoplastic glomerulocystic disease
- ADPKD
- JN + hepatic fibrosis
- multiple malformation syndromes
  - Zellweger's syndrome
  - trisomy 13
  - Meckel's syndrome
  - short-rib polydactyly (Majewski type)
  - TS
  - orofaciogigital syndrome type I
  - brachmesomelia renal syndrome
  - renal-hepatic-pancreatic dysplasia

### What is sporadic glomerulocystic disease?

- noninheritable condition causing bilaterally enlarged kidneys w/ small cysts, predominantly of Bowman's space
  - no other family members affected
  - no associated anomalies
- cysts of glomeruli or Bowman's space present diffusely and bilaterally
  - cysts of glomeruli present in many diseases

### What is acquired renal cystic disease?

- cystic disease occurring in end-stage kidneys

### How can one grade ARCD?

- Thompson (1988)
  - Grade 1: < 5 cysts bilaterally
  - Grade 4: > 14 cysts bilaterally

### What is the incidence of RCC in association w/ ARCD?

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- 34%
  - RCC in 10% of pts on chronic HD
  - if RCC occurs in ESRD, 80% associated w/ ARCD
  - if RCC associated w/ ARCD, occurs at an earlier age

### How is RCC occurring in ESRD different from classic RCC?

- age at occurrence 5 yrs younger in ESRD
- M:F ratio significantly greater in ESRD (7:1 vs. 2:1)
- incidence of RCC in ESRD 3-6X general pplx, 10X in blacks
- if no RCC occurs in 10 yrs after starting HD, unlikely to occur

### Describe the incidence of ARCD.

- in M, usually more advanced
- blacks and Japanese more prone to develop ARCD
- 23% incidence in children on HD
- higher in pts w/ ESRD from nephrosclerosis than DM

### What are the potential causes of ARCD?

- toxins
  - usually multiple and bilateral
  - regress after transplant
  - if transplant fails, cysts return
- loss of functioning renal tissue leads to production of renotropic agents that induce hyperplasia

### What are the features of ARCD?

- Clinical
  - loin pain, hematuria, or both
    - hematuria in 50%
- Histologic
  - cysts occur in cortex, but medulla may be affected
  - usually bilateral
  - 5-10mm in diameter
  - filled w/ clear, straw-coloured, or hemorrhagic fluid
    - may contain Ca oxalate crystals
  - nuclei of epithelial cells are round and regular, w/o prominent nucleoli
    - some cysts may have larger irregular nuclei w/ mitoses
    - hyperplastic lining: may be malignant precursor
  - cysts begin as dilations or outpouching of nephrons
    - may be due to Ca oxalate crystals
  - renal adenomas: usually multiple and bilateral
    - cells oriented into papillary projections or arranged as solid nodules w/ tubule formation
    - nuclei small, rounded, w/ insignificant nucleoli
    - if < 1cm, usually adenoma – if > 3cm, usually RCC
      - ◆ malignant transformation is low

### What is involved in the evaluation of the pt w/ ARCD?

- US: used for dx and monitoring
  - small hyperechoic kidneys w/ various sized cysts
  - suspect infection if internal echoes or thickened wall
- CT
  - may identify cyst wall thickening
  - if pt on HD, give contrast to look for enhancement
- r/o ADPKD
  - pts w/ ARCD have smaller kidneys and smaller cysts, no extra-renal manifestations of ADPKD

### How does one treat the pt w/ ARCD?

- hematuria w/ HD: switch to PD
  - embolization, nephrectomy
- infected cyst: perc drain, open drain, nephrectomy
- monitor all pts on HD for > 3 yrs

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- US and CT initially, then US q6mo
- screen pts if known RF
  - prolonged HD
  - presence of ARCD
  - male
- renal transplantation
  - risk of RCC does not decrease after transplant

### **What is a calyceal diverticulum?**

- smoothly outlined, intrarenal sac that communicates w/ pelvicalyceal system by narrow neck
- lined w/ smooth layer of transitional epithelium, covered w/ thin patch of cortex
- usually arises from fornix of a calyx
  - usually upper pole

### **What is the difference b/w a calyceal diverticulum and pyelogenic cyst?**

- location of communication
  - calyceal diverticulum: communicates w/ a calyx or infundibulum
  - pyelogenic cyst: communicates w/ renal pelvis

### **What is the etiology of calyceal diverticulum?**

- unknown
  - achalasia of the calyceal neck
  - inflammatory stricture of the infundibulum
  - rupture of a solitary cyst

### **What is the treatment of calyceal diverticulum?**

- usually asymptomatic, no treatment
  - if stones present, PCNL and ablation

### **What is the difference b/w parapelvic and renal sinus cysts?**

- cell of origin
  - parapelvic cyst: simple parenchymal cysts around the renal pelvis or renal sinus
  - renal sinus cyst: all other cysts in the hilum, not derived from parenchyma of kidney
    - derived from other structures of sinus: arteries, lymphatics, fat
- most multiple cystic structures in renal sinus are lymphatic cysts
- most singular cysts will be derived from renal pelvis

### **What is the predominant type of renal sinus cyst?**

- derived from lymphatics
  - usually multiple and bilateral
  - appear after age 50
  - may be associated w/ inflammation, obstruction, stone

### **What is polycystic disease of the renal sinus?**

- entity w/ benign natural hx (except for stones)
- radiolucencies seen in renal sinus, w/ stretching of the infundibula
  - looks like renal sinus lipomatosis

### **What is the DDx of bilateral renomegaly and renal cysts?**

- ARPKD
- ADPKD
- TS
- VHL
- bilateral simple cysts
- sporadic glomerulocystic renal disease
- ARCD



## Chapter 57

### • Anomalies and Surgery of the UPJ in Children •

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*-Please refer to chapter 13 (UPJ in adults)*

**What is the most common cause of hydronephrosis in the fetal kidney?**

- UPJO
  - 48% of all dilation

**Describe the epidemiology of UPJO.**

- M > F
- L > R
- bilateral in 10-40%

**What are the potential etiologies of UPJO?**

- Intrinsic
  - narrowed segment of ureter
    - due to interruption of circular development of UPJ or alteration of collagen development
    - muscle fibers become widely separated and attenuated → leads to functional discontinuity of muscular contractions
  - congenital valvular mucosal folds: "Östlings folds"
    - due to differential growth rates of ureter and body of child: not obstructive, disappear w/ linear growth
  - persistent fetal convolutions
  - upper ureteral polyps
  - ureteral stricture
  - urothelial malignancy
  - stones
  - postinflammatory or postop scarring
- Extrinsic
  - aberrant, accessory, or early branching vessel: most common cause (15-50%)
    - cross the ureter **posteriorly**
    - 2 pt obstruction: as vessel touches ureter, and further angulation at UPJ due to scarring
  - external adhesions
  - high insertion of ureter into renal pelvis: may be a secondary phenomenon seen
- Secondary
  - severe VUR (10% of cases)
- precise cause unknown

**What anomalies are associated w/ UPJO?**

- congenital renal malformations: most common
  - contralateral UPJO
  - renal dysplasia
  - MCDK
  - unilateral renal agenesis: 5%
  - duplicated collecting system
  - horseshoe kidney
- VUR: 40%
- VACTERL association: 20%

**What are the sx of UPJO?**

- infants: asymptomatic
  - may have palpable mass
- children: most have sx



## Chapter 57 Questions - UPJO.doc

- episodic flank or upper abdominal discomfort
- N/V, cyclic vomiting
- hematuria: 25%
  - after minor abdo trauma: due to disruption and rupture of mucosal vessels in dilated collecting system
- htn

### What studies can be used to dx UPJO?

- US
  - does not diagnose obstruction, only shows if hydro worsening
  - renal parenchyma/pelvic/collecting area  $< 1.6$  correlates w/ obstruction
  - Doppler RI values higher ( $>0.75$ ) in obstructed kidneys
- MRI
  - can show RBF, anatomy, and excretion
- radionuclide renography
  - DTPA: eliminated entirely by filtration: indirect measure of GFR
  - MAG3: cleared primarily by tubular secretion, less by filtration → measure of effective renal plasma flow
- Whitaker test
  - ureteral opening pressure = pressure at which contrast first seen beyond the area of obstruction
  - renal pelvis pressure  $> 14$  cm H<sub>2</sub>O demonstrates obstruction
- labs: urinary NAG (N-acetyl- $\beta$ -D-glucosaminidase), TGF- $\beta$ 1 increased in obstruction

### What are the indications for intervention in UPJO?

- **presence of sx** associated w/ obstruction
- impairment of overall **renal function**
- development of **stones** or **infection**
- **hypertension**
- **solitary kidney** or **bilateral** disease

### What are the different ways to surgically repair UPJO?

- flap type procedures
  - Foley V-Y plasty
  - Culp-DeWeerd spiral flap
  - Scardino-Prince vertical flap
- incisional-incubated type procedures
  - Davis intubated ureterotomy
- dismembered type procedures
  - dismembered pyeloplasty (Anderson-Hynes)
- lap/endourologic procedures
  - retrograde endoscopic pyelotomy
  - cautery wire balloon endopyelotomy
  - percutaneous pyelotomy
  - lap pyeloplasty
- salvage procedures
  - ureterocalycostomy

### Describe the technique of dismembered pyeloplasty.

- Pre-op
  - retrograde pyelogram: r/o concomitant UVJO
  - incision choice
    - do not use dorsal lumbotomy if abnormal retrograde or in muscular youth
- Procedure
  - anterior subcostal incision: muscle splitting
  - identify Gerota's fascia, which is incised posteriorly over lateral aspect of kidney
  - renal pelvis identified by medial retraction of peritoneal and lateral traction on kidney
    - decompress renal pelvis w/ needle if needed
  - traction suture in renal pelvis to minimize handling
  - dissect out UPJ, traction suture superiorly
  - confirm ureteral length, transect ureter at UPJ
    - mobilize kidney if needed
  - ureter spatulated opposite to traction suture

## Chapter 57 Questions - UPJO.doc

- excise redundant pelvis: diamond shaped segment within traction sutures
  - better to leave too much renal pelvis than too little
- ureter and renal pelvis aligned
- place NT
- anastomosis of ureter to neo-UPJ
- irrigate renal pelvis free of blood clot
- place ureteral stent
- JP drain
- return kidney to native position
- close fascia
- Post-op
  - Foley
  - nephrostogram 14d postop
  - stent x 6-8 weeks, US at 6 weeks
  - renal scan 1 year post-op
  - imaging at 3 yrs

### What are the results after pyeloplasty for UPJO?

- success defined as improvement of hydro and stabilization or improvement in function, resolution of sx
- success generally > 90%

### What are the complications of pyeloplasty?

- Intraop
  - bleeding, transfusion: not reported
  - bowel injury
- Postop: Early
  - prolonged urinary leakage: observation initially, retrograde stenting, NT → redo, ureterocalycostomy if needed (wait > 2 months until attempt)
  - recurrent obstruction
  - urinoma





## **Chapter 58**

### **• Ectopic Ureter, Ureterocele, and Other Anomalies of the Ureter •**

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#### **What is meant by the following terms:**

- duplex kidney: 2 separate pelvicalyceal systems
  - upper and lower pole
  - ureters may join at any point
- bifid system: ureters join at level of UPJ
- double ureters: ureters drain respective poles and empty separately into GU tract
- lateral ectopia: orifice more lateral and cranial than normal
- caudal ectopia: orifice more medial and caudal than normal
- ectopic ureter: ureter whose orifice terminates even more caudally → in urethra, or outside GU tract

#### **How can one classify ureterocele?**

- Ericsson
  - simple = one that lies completely within the bladder
  - ectopic = extended to BN or distally to urethra
- Stephens
  - stenotic = narrowed or pinpoint opening found inside the bladder
  - sphincteric = orifice distal to BN
  - sphincterostenotic = orifice both stenotic and distal to BN
  - cecoureterocele = intravesical orifice and submucosal extension that dips into the urethra
- Committee on Terminology, Nomenclature, and Classification of the Section of Urology of the AAP
  - intravesical vs. ectopic
    - intravesical = ureterocele contained within the bladder in its entirety
    - ectopic = any portion of the ureterocele extends to BN and urethra
  - single vs. duplex
  - type of orifice involved

#### **How does ureteral ectopia affect renal function?**

- renal units drained by ectopic ureters have problems w/ proper development
  - ureteric bud poorly positioned for proper interactions w/ metanephric blastema

#### **What is the cause of primary VUR?**

- lateral ectopic ureter
  - ureter has submucosal course that is short and almost perpendicular to the bladder wall
    - prevents normal operation of the flap valve
  - trigone is large and poorly muscularized
  - intramural ureter is deficient in musculature

#### **Describe the epidemiology of ectopic ureter.**

- 80% associated w/ duplicated collecting system
- F: > 80% duplicated
- M: most ectopic ureters drain a single system
- F > M

#### **What are the potential drainage sites for ectopic ureters?**

- M
  - posterior urethra: 47% → most common site of termination
  - SV: 33%
  - prostatic utricle: 10%
  - ED, vas: 5% each
- F

## Chapter 58 Questions - Ureterocele.doc

- urethra: 35% → most common
- vestibule: 34%
- vagina: 25%
- cervix or uterus: 5%
- Gartner's duct: <1%
- urethral diverticulum: <1%

### What is the clinical presentation of ectopic ureters?

- differs b/w M and F
  - F: continuous incontinence
  - M: UTI (epididymitis)
- abdo pain, FTT, UTI
- abdominal mass
- stone in ectopic ureter

### How can ectopic ureter cause incontinence in females and not in males?

- ureteric bud arises more proximally on mesonephric duct
  - ureteric orifice remains on mesonephric duct more caudally, and is not absorbed into the bladder
- F: becomes incorporated into epoophoron, oophoron, and Gartner's ducts
  - can rupture into or become incorporated into vagina, uterus, cervix, tubes
- M: becomes incorporated into BN, prostatic urethra, vas
  - all proximal to EUS → cannot cause UI like in F

### How can one diagnose ectopic ureters?

- Hx/Px
  - UI, infection, pain, hematuria
  - direct visualization of the vulva: dribbling, wetness, punctum or orifice
- US
  - hydronephrosis w/ normal bladder
  - thin renal parenchyma
- IVP
  - pay attention to contralateral kidney: bilateral ureteral ectopia in 5-17%
- DMSA
  - important if need to salvage upper pole
- VCUG
  - demonstrates VUR into lower pole ureter in > 50%
    - if VUR seen prior to voiding, UO is proximal to BN
    - if VUR seen only w/ voiding, UO in urethra
- Cysto/vaginoscopy
  - may visualize ectopic UO, with help w/ 2 doses Pyridium day prior to cysto

### What are the signs of ureteral duplication on IVP?

- nonvisualizing or poorly visualizing upper pole of a duplex system
- upper pole displaces lower pole down and out = "drooping lily" appearance
- calyces of a lower pole fewer in number than in normal kidney
- axis of lowest to uppermost calyx does not point towards midline
- uppermost calyx of the lower pole unit is farther from the upper pole border than is the lowest calyx from the corresponding lower pole limit
- lower pole pelvis and upper portion of its ureter may be farther from the midline than contralateral kidney
- lower pole ureter may be scalloped and tortuous due to wrapping around a dilated upper pole ureter

### What is the difference b/w a ureterocele and pseudoureterocele?

- pseudoureterocele = ectopic ureter, clearly extravesical w/ thick septum of bladder muscle b/w ureteral lumen and bladder lumen
- ureterocele = septum is thin, ureteral lumen partially intravesical

### What is the treatment of ectopic ureters?

- upper pole nephrectomy
  - most ectopic ureters drain upper poles w/ minimal function
    - may be worth salvaging, esp. if single system ectopic ureter

## Chapter 58 Questions - Ureterocele.doc

- flank approach has better exposure to upper pole vessels
- transect upper pole ureter and place traction stitch on proximal portion
- maintain dissection on wall of upper pole ureter to prevent ischemia of lower pole ureter
- may be necessary to remove ectopic ureter if concomitant VUR exists
- ureteropyelostomy
- common sheath ureteral reimplantation

### What is the typical configuration for bilateral single-system ectopic ureter?

- ureters drain in to prostatic urethra (M) or distal urethra (F)
- no formation of trigone
- wide, poorly defined incompetent BN
  - may be agenesis of bladder and urethra
- bilateral aplastic/dysplastic kidneys +/- hydro
  - dilated ureters, +/- VUR
- continuous dribbling
- small capacity bladder
- UOs identified just distal to BN
- short urethra

### What is a ureterocele?

- cystic dilation of the terminal ureter

### What are the proposed theories for etiology of ureterocele?

- incomplete dissolution of Chwalla's membrane
- abnormal muscular development
- developmental stimulus responsible for bladder expansion works simultaneously on intravesical ureter

### Describe the epidemiology of ureteroceles.

- F:M 4:1
- almost exclusively whites
- 10% bilateral
- 80% arise from upper pole of duplex systems

### What are the sx of ureterocele?

- UTI or urosepsis
- stone
- palpable mass (hydronephrotic kidney)
- vaginal mass (prolapsed ureterocele)
- obstruction of contralateral kidney
- incontinence: interference w/ BN
- hematuria
- FTT
- abdo/pelvic pain

### How can one diagnose ureterocele?

- US
  - associated duplex kidney
    - varying degrees of thickness and echogenicity
  - dilated ureter from hydronephrotic upper pole
  - lower pole may be hydronephrotic if VUR present
  - bladder: thin-walled cyst that is the ureterocele
    - if overdistended, ureterocele effaced and is not visible
- IVP
  - poorly functioning upper pole
- VCUG
  - VUR into ipsilateral lower pole: 50%
  - VUR into contralateral lower pole if ureterocele large enough to distort the trigone
  - may evert into ureter and appear as diverticulum
  - filling defect seen in bladder: "cobra-head", or "spring-onion" deformity

## **Chapter 58 Questions - Ureterocele.doc**

- DMSA  
→ estimate of upper pole function

### **What are the goals in treatment of ureterocele?**

- preservation of renal function  
→ preservation of renal parenchyma
- elimination of UTI, obstruction, and VUR
- maintenance of continence
- minimizing surgical morbidity

### **What are the different treatment approaches for ureterocele?**

- upper tract approach = upper pole nephrectomy + partial ureterectomy or ureteropyelostomy  
→ 20-60% need secondary procedures
- combined approach = upper pole nephrectomy, ureterocele excision, and lower pole reimplantation  
→ 14% required 2<sup>nd</sup> procedure, usually for VUR

### **What are the indications for each approach for ureterocele?**

- Upper tract approach  
→ low-grade or no VUR into ipsilateral lower pole  
→ ureteropyelostomy or u-u: need for salvage of upper pole
- Combined approach  
→ those infants w/ high likelihood of requiring 2<sup>nd</sup> procedure for VUR:
  - high grade VUR +/- hydro into ipsilateral lower pole ureter
  - lower pole VUR into lower pole w/ large everting ureterocele and poorly functioning upper pole
  - prolapsed ureterocele
  - contralateral kidney w/ significant hydro +/- VUR  
→ septic pts not responding to antibiotics → treat initially w/ endoscopic incision

### **What are the advantages of the upper tract approach for treatment of ureterocele?**

- decompression of ureterocele + resolution of VUR w/ return of trigone to normal configuration
- avoidance of morbidity of 2<sup>nd</sup> surgical procedure
- elimination of difficult BN and urethral dissection

### **Describe the technique of excision of ectopic ureterocele and common sheath reimplantation.**

- bladder opened
- stay sutures placed
- ureterocele incised in transverse direction
- posterior mucosal wall of ureterocele is incised transversely
- incision continued around bladder mucosal edge of ureterocele, including lower pole orifice
- upper and lower pole ureters mobilized
- distal ureterocele retracted caudally
- dilated upper pole tapered
- both ureters brought into bladder through new muscular hiatus
- thinned posterior bladder wall repaired w/ interrupted sutures for adequate muscular backing for ureters
- ureters reimplanted into new mucosal tunnel  
→ lower pole orifice is medial

### **What is the problem w/ distal u-u in the upper tract approach?**

- yo-yo effect  
→ urine boluses down one ureter, w/ retrograde flow up other ureter  
→ decreases urinary drainage, leading to stasis, UTI, and dilation

### **What are the results after endoscopic treatment of ureterocele?**

- difference in success of incision based on type of ureterocele
- intravesical ureteroceles fare better than ectopic ureterocele
  - decompression: 93% vs. 75%
  - preservation of upper pole function: 96% vs. 47%
  - new VUR: 18% vs. 47%
  - need for 2<sup>nd</sup> procedure: 7% vs. 50%

## **Chapter 58 Questions - Ureterocele.doc**

### **What are the indications for endoscopic incision of ureterocele?**

- controversial
  - intravesical ureterocele
  - ectopic ureterocele causing BOO or sepsis

### **Why must one pass the cystoscope under direct vision in a pt w/ ureterocele?**

- may tear ureterocele

### **Describe the method of ureterocele incision.**

- transverse incision through full thickness of ureterocele wall using cutting current
  - ectopic ureter into urethra: longitudinal incision that extends down from intravesical portion into urethral portion, or 2 separate punctures
- make incision as distal as possible, as close to bladder floor as possible → decreased chance of VUR into ureterocele
- incise deeply: may be thick walled

### **What is the difference in the characteristics of single-system ureteroceles vs. those associated w/ duplex kidneys?**

- degree of obstruction tends to be less severe
- more amenable to endoscopic incision

### **What are the features of a prolapsed ureterocele?**

- smooth round wall
- pink/red → brown, purple, blue
- slides down posterior wall of urethra
- vagina posterior to ureterocele
- BOO may be present

### **What is the treatment of prolapsed ureterocele?**

- initially: decompression of ureterocele w/ manual reduction of ureterocele
  - transverse incision at level of vagina if pt acutely ill
  - open surgical unroofing or marsupialization
- upper pole nephrectomy + aspiration of ureterocele

### **In order of frequency, what areas of the ureter are most commonly associated w/ congenital stenosis?**

- distal ureter just above extravesical junction
- UPJ
- midureter at pelvic brim

### **What are ureteral valves?**

- transverse folds of redundant mucosa that contains smooth muscle
- single annular or diaphragmatic lesions w/ pinpoint opening
- ureter dilated above the obstruction, normal below it

### **What are the most common areas to find ureteral valves?**

- throughout the length of the ureter
  - least commonly in middle 1/3 or UPJ

### **What are the sx of ureteral valves?**

- flank pain, UTI, UI, htn, hematuria

### **How can one classify ureteral diverticulae?**

- abortive ureteral duplications
  - blind ending bifid ureters
- true congenital diverticulae containing all layers of the normal ureter
- acquired diverticulae representing mucosal herniations

### **What is the incidence of ureteral duplication?**

- 1 in 125 (0.8%)
  - unilateral: 77-86%
  - bilateral: 14-23%
  - complete 29-77%



## Chapter 58 Questions - Ureterocele.doc

- R = L
- AD trait w/ incomplete penetrance: increased incidence w/ 1<sup>st</sup> degree relative (1 in 8)

### What embryonic theory may explain the rare exceptions to the Weigert-Meyer law?

- upper pole orifice located craniomedially arises from junctional ureteric bud, one that bifurcated immediately, rather than a 2<sup>nd</sup> bud

### What findings are associated w/ ureteral duplication?

- GU
  - increased # calyces (11.3 vs. 9.4 in single-system units)
  - VUR
  - hydro of lower pole: usually due to severe VUR
    - may be due to UPJO
  - renal hypoplasia and aplasia/dysplasia
  - ectopic insertion of upper pole ureter
  - UTI
- GI or CVS/pulm lesions

### What is the treatment of bifid ureter?

- often clinically unimportant
  - treat if stasis and pyelo occur
  - reimplantation of common sheath if junction close to bladder
  - reimplantation of common stem if junction higher up
  - ureteropyelostomy or pyelopyelostomy w/ resection of upper limb to level of bifurcation

### Describe the epidemiology of blind-ending duplication of the ureter.

- rare: < 70 cases reported
- may be at any level: usually in mid- or distal ureter
- F:M 3:1
- R:L 2:1

### What are the sx of blind-ending duplication of the ureter?

- abdo or chronic flank pain
- infection, stone

### What is the cause of blind-ending duplication of the ureter?

- abortive ureteric bud
  - fails to make contact w/ metanephros

### What is the difference b/w a blind-ending ureter and a ureteral diverticulum?

- may be a matter of terminology
  - blind ending segment of a Y ureter joins normal ureter at acute angle
    - 2X as long as it is wide
  - congenital diverticulum has a ballooned appearance

### What is the most rare form of ureteral branching?

- inverted Y ureteral duplication
  - 2 ureteral limbs distally that fuse proximally to form a single channel
  - one end often ends in ectopic ureter or ureterocele
- 2 separate ureteric buds whose tips coalesce and fuse into a single duct before joining the metanephros

### How can one classify the varieties of triplicate ureter?

- complete triplication: 3 ureters from kidney, w/ 3 UOs
- incomplete triplication: bifid ureter + single ureter, w/ 3 ureters from kidney and 2 UOs
- trifid ureter: all 3 ureters unite and drain in single UO → most common form
- 2 ureters from kidney, one becoming an inverse Y bifurcation, w/ 3 UOs

### What is the typical configuration of the preureteral vena cava (or retrocaval ureter)?

- usually R ureter
  - deviates medially behind (dorsal) IVC, crossing in front of it from medial to lateral

## Chapter 58 Questions - Ureterocele.doc

→ renal pelvis and upper ureter elongated and dilated in J or fishhook shape

### What are the different types of retrocaval ureter?

- Type I: more common
  - fish-hook shape deformity, w/ hydro and obstruction
- Type II
  - less hydro or none at all
  - upper ureter not kinked

### Describe the embryologic formation of a preureteral vena cava.

- IVC develops on R side from fetal plexus of veins
  - posterior cardinal and supracardinal veins lie dorsally
  - subcardinal veins lie ventrally
- normally, L supracardinal veins and lumbar portion of R posterior cardinal vein atrophy
  - subcardinal veins become gonadal veins
  - IVC forms from R supracardinal vein
- if **R subcardinal vein fails to atrophy** and becomes the predominant R-sided vein, the ureter is trapped dorsally
  - if subcardinal and supracardinal vein both persist, double R IVC forms, trapping ureter b/w

### What is the incidence of retrocaval ureter?

- 1 in 1500
  - M:F 4:1

### How can one diagnose retrocaval ureter?

- IVP
  - failure of visualization of ureter beyond J hook
- retrograde pyelogram
  - S curve to level of obstruction
  - retrocaval ureter lies at level of L3-4
- CT

### What is the treatment of retrocaval ureter?

- surgical correction
  - relocation w/ u-u and excision of retrocaval segment

### Describe the embryologic formation of a preureteral iliac artery (retroiliac ureter).

- normally: primitive ventral root of umbilical artery replaced by development of a more dorsal branch b/w aorta and distal umbilical artery
- persistence of ventral root as dorsal root fails to form traps the ureter dorsally

### What is the typical configuration of ureteral herniation?

- most paraperitoneal
  - loop of herniated ureter extends alongside peritoneal hernial sac
  - ureteral loop always medial to peritoneal sac
- minority extraperitoneal w/ no hernial sac present





## **Chapter 59**

### **• Vesicoureteral Reflux and Megaureter •**

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#### **What is the general incidence of VUR?**

- 10% in general population
- 70% of pts that present w/ UTIs

#### **What are RF for having VUR?**

- male sex (if young + UTI)
  - uncircumcised males 10X more likely to get UTI during 1<sup>st</sup> few months of life
- prenatally diagnosed hydronephrosis: 37%
- young age
- Caucasian: 10X more likely than blacks
  - once VUR discovered, chance of resolution is similar
- sibling w/ VUR

#### **How does prenatally diagnosed VUR differ in boys vs. girls?**

- VUR usually high grade and bilateral in boys compared w/ girls
  - fetal VUR associated w/ high degree of resolution, even w/ high grades

#### **What is the incidence of VUR in kids w/ UTI?**

- age dependent, highest in young children:
  - <1: 70%
  - 4 yrs: 25%
  - 12 yrs: 15%
  - adults: 5.2%

#### **What is the risk of developing VUR in a sibling of a child w/ VUR?**

- siblings of pts w/ VUR are at much higher risk of developing VUR
  - up to 45% have VUR
  - 75% are asymptomatic
  - no relation b/w grade of VUR b/w sibs
  - greater incidence of sibling VUR in pts w/o bladder dysfunction vs. with bladder dysfunction (40% vs. 20%)
  - ?dominant pattern w/ variable penetrance
- 80% in identical twins, 35% of fraternal twins

#### **What are the current recommendations for screening siblings of children w/ VUR?**

- US/VCUG for babies and young children, esp. if < 5 yrs
- in older sibs, RBUS only
  - if RBUS abnormal (hydro, scarring, discrepancy in renal size) or if UTIs, obtain VCUG

#### **How does the UVJ prevent VUR?**

- when a bolus of urine reaches the hiatus, the intravesical muscles contract
- pulls orifice toward the hiatus to shorten and widen the intravesical ureter, reducing resistance
- after ureter relaxes, passive "flap-valve" mechanism prevents VUR during bladder filling

#### **What factor is most critical to a competent UVJ?**

- length of submucosal tunnel relative to diameter
- 5:1 ratio seen in N kids w/o reflux

#### **What is the etiology of VUR?**

- Primary VUR
  - deficiency of longitudinal muscle of the intravesical ureter results in an inadequate valvular mechanism

## Chapter 59 Questions - VUR.doc

- lack of 5:1 ratio of length:width
- Secondary VUR
  - PUV: most common cause
    - associated w/ VUR in 50% of pts w/ PUV
  - ureterocele
  - UTI: ureteral atony caused by gram -ve endotoxins
    - lessens compliance, increases intravesical pressures, and distorting and weakening the UVJ
    - transient VUR can appear during UTI and resolve after tx
  - cyclophosphamide: cystitis → similar to UTI
  - urethral stenosis
  - meatal stenosis
  - functional causes: neurogenic bladder, non-neurogenic neurogenic bladder, bladder instability or dysfunction
    - spina bifida, sacral agenesis

### What is the most common urodynamic finding in a child w/ VUR?

- uninhibited bladder contractions: seen in 75% of girls w/ VUR

### What is the success of treating neurologically intact children that have VUR w/ anticholinergics?

- if have uninhibited bladder contractions: 44%
- if normal bladder function: 17%

### What therapeutic options are available for kids w/ residual urine and VUR?

- double voiding
- relaxation techniques or biofeedback
- IC + medication

### When a child presents w/ a UTI, when should one do the VCUG?

- controversial
  - may defer for a few weeks to allow inflammation to abate and avoid pain, false +ve
  - may miss VUR that occurs only w/ UTI: may perform if have had antibiotics for a few days

### How does one classify VUR?

- International Classification System (ICS): 1981 by IRSC
  - Grade I: into a nondilated ureter
  - Grade II: into a nondilated renal pelvis
  - Grade III: mild dilation of ureter, mild blunting of renal fornices
  - Grade IV: moderate ureteral dilation or tortuosity, flattening of renal fornices
  - Grade V: gross dilation of ureter, ureteral tortuosity, gross dilation of renal pelvis and fornices, loss of papillary impression
- grading VUR is impossible if there is ipsilateral ureteral obstruction
- grading VUR w/ RNC is difficult: can only differentiate b/w Grade I or Grade II and up

### How do patients present w/ VUR?

- usually UTI
  - newborns: FTT, lethargy, fevers
  - infants, young kids: fever, foul smelling urine, dysuria, LUTS, lethargy, GI sx
  - children and adults: abdo or flank pain
- fever
  - if fever present, likelihood of VUR greatly increased
  - VUR present in 56% of pts < 6mo w/ T > 38.5

### Name some markers that have been investigated as potential markers for localizing infection to the upper tracts.

- beta-2 macroglobulin
- LDH
- antibody-coated bacteria
- IL6, IL8
- antibodies to Tamm-Horsfall protein, NAG, ICAM-1, EGF

### How can one document a UTI in a child?

- MSU if toilet trained

## Chapter 59 Questions - VUR.doc

- growth of  $> 10^5$  CFU/HPF is significant
- catheterized specimen or SP aspiration
  - preferred if suspect contaminated specimen
  - growth of  $> 10^4$  CFU/HPF is significant

**True or false: renal scarring can occur w/ a single UTI, even in the absence of a fever.**

- true

**Which groups of patients w/ UTI will require a complete evaluation (VCUG and RBUS)?**

- any child  $< 5$  w/ a documented UTI
- any child w/ febrile UTI, regardless of age
- any boy w/ UTI (unless sexually active or has a past urologic history)
- groups that do not require full workup:
  - older children that present w/ asymptomatic bacteriuria or simple UTI w/o fever: US only initially
  - black children: full workup if recurrent or febrile UTI → low incidence of VUR

**Which groups of children w/ antenatally detected hydronephrosis should be investigated?**

- newborns w/ moderate to severe upper tract dilation should be fully evaluated w/ VCUG
- any baby w/ intermittent hydro as a fetus

**What is the natural hx of pts w/ antenatally detected hydronephrosis?**

- 15% of all antenatally detected hydro is VUR
  - 60% resolve
  - 10% of pts w/ antenatally detected VUR develop UTIs
  - 2% develop scars

**What can cause a false –ve VCUG in a child w/ VUR?**

- child that has VUR only during voiding, and refuses to void during test
- excessive hydration: diuresis may blunt retrograde flow of urine
- VUR that is present only during UTI

**What can cause a false +ve VCUG?**

- cystogram done under GA: bladder overfilling
- UTI: gram –ve endotoxins can paralyze ureteral smooth muscle and exaggerate ureteral dilation

**What are the potential options for cystography?**

- fluoroscopic VCUG
- cyclic VCUG
- RNC
- indirect cystography (w/ DTPA)
  - unreliable: high # of false –ve
- US cystography

**What are the advantages and disadvantages of an RNC?**

- does not provide anatomic detail
- minimizes radiation exposure: 100X less
- enhanced sensitivity for Grade I reflux

**What is a cyclic VCUG and when is it done?**

- repeat VCUG several times w/ several cycles of filling and voiding
- indicated in patients w/ strong suspicion of reflux not demonstrated on the first VCUG

**What should always be done during an upper tract functional study in patients w/ VUR?**

- place a Foley
  - contrast from the contralateral side can reflux into a nonfunctioning upper pole, mimicking function

**What are the potential options for assessing the upper tract in a patient w/ VUR?**

- US
- doppler US

## **Chapter 59 Questions - VUR.doc**

- IVP
- SPECT
- DMSA

### **What finding on US can suggest VUR?**

- intermittent dilation of the renal pelvis or ureter

### **What findings on IVP suggest the presence of VUR?**

- scarring w/o obstruction
- renal growth retardation
- retrograde ureteral jet

### **What is the role of DMSA in the evaluation of a child w/ UTI?**

- unclear
  - may be used to document pyelonephritis
  - sensitive in detecting renal scarring
  - some people use to screen patients w/ known reflux q2yearly

### **What are the relative indications for cystoscopy immediately before reimplantation in a child w/ VUR?**

- nonvisualization of the entire urethra on VCUG
- uncertainty in ureteral location or anomaly: duplication, ectopia, ureterocele
- inconclusive radiographic definition of lower or upper tract anomalies
- localization of paraureteral diverticulum
- ?suspected active UTI

### **What is the value of orifice configuration in predicting presence of VUR?**

- little value
- spectrum from medial → lateral (increased risk of VUR): normal/cone, stadium, horseshoe, golf-hole

### **What are the radiologic changes seen in a kidney w/ reflux nephropathy?**

- focal thinning of renal parenchyma overlying a clubbed distorted calyx
- generalized calyceal dilation w/ parenchymal atrophy
- impaired renal growth, w/ either focal scarring or global atrophy

### **What is the relationship b/w the grade of VUR and the incidence of reflux nephropathy?**

- direct relationship
  - Grade I VUR: 5% had reflux nephropathy
  - Grade II: 6%
  - Grade III: 17%
  - Grade IV: 25%
  - Grade V: 50%

### **What factors determine the severity of renal injury w/ VUR?**

- grade of VUR
- age of pt
  - risk of scarring greatest in kids < 1yr
  - scars rarely form after age 5
  - most scars occur w/ 1<sup>st</sup> infection
- anatomic considerations
  - compound papillae more likely to get scars: due to R angle of collecting duct → usually in poles
- bacterial virulence factors
  - O antigen, K antigen, MRHA, P pili, P blood group ligands (P1 blood group), Lewis (a-b-)
- host susceptibility
  - degree of preputial and vaginal bacterial colonization
  - regular effective bladder emptying: most important defense against UTI
- inflammatory response to infection
  - activation of complement, renal ischemia and reperfusion, release of free radicals, microabscesses
- early dx and effective antibiotic treatment

### **What is the most common cause of severe htn in children and young adults?**

## Chapter 59 Questions - VUR.doc

- reflux nephropathy: 38%
  - arterial damage due to renal scarring → segmental ischemia and activation of RAAS
  - elimination of VUR does not reverse risk of htn once scarring present

### What factors contribute to the effects of VUR on renal growth?

- congenital dysmorphism
- UTI: type and #
- quality of contralateral kidney → compensatory hypertrophy
- grade of VUR in affected kidney
- antireflux surgery
  - can accelerate renal growth, but may not allow kidney to reach normal size

### What anomalies are associated w/ VUR?

- UPJO
  - VUR present in 5-25% of pts w/ UPJO
  - UPJO present in 0.8-14% of pts w/ VUR
  - high-grade VUR may cause secondary UPJO w/ kinking of upper ureter
- ureteral duplication
  - VUR usually involves ureter from lower pole → lateral position and shorter submucosal tunnel
  - frequency of resolution of VUR same in pts w/ single or double ureters
- bladder diverticula
  - occur w/ Ehlers-Danlos syndrome, Menkes' syndrome
  - most common location: lateral and superior to UO
  - usually prolapse outside bladder, altering UVJ anatomy
  - VUR from small diverticulae usually resolves, but large diverticulae less likely to resolve → needs OR
    - when ureter enters diverticulum → OR recommended
- renal anomalies
  - renal agenesis
  - MCDK
- megacystis-megaureter association
  - massive bilateral VUR w/ marked dilation of ureters and bladder
  - thin bladder wall, absence of BOO
  - needs OR
- VACTERL association
- CHARGE syndrome
  - coloboma, heart disease, atresia choanae, retarded development, genital hypoplasia, ear anomalies
- imperforate anus

### What are the signs of secondary UPJO from VUR on VCUG?

- impaired/absent filling of renal pelvis by VUR that causes dilation of ureter below UPJ
- prompt drainage from ureter w/ retention of contrast in renal pelvis on post-void films
  - adequate drainage from renal pelvis will r/o UPJO

### What is the treatment of secondary UPJO from VUR?

- if scintigraphy w/ catheter drainage documents obstruction → pyeloplasty
  - if correct VUR initially, may amplify UPJO from distal ureteral edema
- otherwise, do reimplant

### How does the GU tract change during pregnancy?

- bladder tone decreases
  - due to edema and hyperemia
  - predisposes pt to bacteriuria
- urine volume increases in upper tract
  - due to physiologic dilation

### How does presence of VUR affect pregnancy?

- increased morbidity from infection-related complications
  - higher incidence of pyelonephritis
  - hx of prior UTI: high incidence of bacteriuria during pregnancy
  - women w/ bilateral renal scars have increased risk of preeclampsia vs. unilateral (24% vs. 7%)



## Chapter 59 Questions - VUR.doc

- women w/ htn and renal failure at particularly at risk
- pts w/ VUR should have this corrected prior to pregnancy to decrease maternal and fetal morbidity

### What is the natural hx of VUR?

- depends on initial grade and age at presentation
  - spontaneously resolves in many children
- due to elongation of submucosal tunnel w/ bladder growth, as well as change in bladder dynamics
- normal renal growth if no UTIs
- Grade
  - low grade (I or II): 80-85% resolve spontaneously
  - intermediate grade (III): 50% resolve
  - high-grade (IV or V): 30% or 12% resolve
- Age
  - younger children more likely to have VUR
  - younger children more likely to have spontaneous resolution, regardless of grade
  - usually resolves within 1<sup>st</sup> few yrs after diagnosis
    - uncommon to resolve after age 5
  - absence of improvement on serial cystograms: resolution may not occur

### Is there a role for conservative management of primary VUR in the era of bulking agents?

- depends on:
  - definition of conservative
  - pt factors: age, sex, grade, renal condition, tolerance/compliance w/ prophylaxis, UTI hx
  - parental factors: feelings about prophylaxis, compliance, visits
  - bulking agent
  - likelihood of resolution

### What is the treatment for VUR?

- No scarring at dx
  - grade I-II VUR: medical management
    - most cases will resolve, even in duplex systems
  - grade III-IV VUR
    - prepubertal children: medical management (esp in younger children w/ unilateral disease)
    - older children: surgery only if bilateral or if does not improve
    - duplex systems less likely to resolve if high grade
  - grade V VUR
    - newborns / young children: medical management initially if able to stay on antibiotics
    - older children: unlikely to resolve
      - ◆ OR recommended after infancy
  - girls w/ persistent VUR: OR
    - prevents complications from future pregnancies
  - older boys: d/c prophylaxis
- Scarring at dx
  - grade I-II: medical management
  - grade III-IV
    - unilateral: medical management
    - bilateral
      - ◆ young children: medical management
      - ◆ older kids: surgery
  - grade V
    - newborns: medical management initially
    - > 1 yr: surgery

### What is involved in the medical management of VUR?

- continuous low-dose prophylactic antibiotics until resolution of VUR
  - suspensions OD at ½ standard therapeutic dose
  - amoxicillin/ampicillin recommended for children up to 6 weeks in age
  - TMP/SMX after 2 months
    - no TMP/SMX prior to 6 weeks of age → kernicterus
  - nitrofurantoin: best suited to minimizing fecal resistance

## Chapter 59 Questions - VUR.doc

- no nitrofurantoin prior to 2 months
- d/c prophylaxis once VCUG shows resolution
- bladder retraining: improved toilet hygiene and bladder emptying
  - timed voids
  - double voiding
  - proper perineal wiping
  - elimination of constipation
- anticholinergic therapy
- periodic urine cultures q3mo
- yearly radiologic studies
  - no need for serial DMSA scans unless recurrent bouts of pyelo w/ scarring suspected
  - no need for confirmatory repeat VCUG

### What are the results of medical management of VUR?

- International Reflux Study in Children: medical and surgical management of high-grade (III or IV) VUR in kids < 9
  - surgery better than medical management in preventing pyelo (10% vs. 21%), but UTIs same (38%)
  - equal at preventing new scarring
  - if dysfunctional voiding present and untreated, pts had more UTIs, more persistent VUR
- Birmingham Reflux study
  - 50-80% of medically treated pts w/ severe reflux had persistence after 5yrs

### What are the indications for antireflux surgery?

- breakthrough UTIs despite prophylactic antibiotics
- noncompliance w/ medical management
- severe VUR (grade IV or V) esp. w/ pyelonephritic changes
- failure of renal growth, new scars, or worsening renal function
- VUR persisting in girls at puberty
- VUR associated w/ congenital abnormalities of the UVJ (bladder diverticulae)

### What are the various ways of surgically correcting VUR?

- Intravesical techniques
  - Politano-Leadbetter
  - Cohen cross-trigonal technique
    - useful in small bladders, thickened bladders → gentler ureteral curve
  - Glenn-Anderson
    - less obstruction or kinking, as ureter remains in original hiatus
    - best candidates are those whose ureters are laterally positioned
  - Gil-Vernet
    - relies on sphincteric action of intrinsic muscular fibers of transmural ureter to prevent VUR
    - intravesical ureter must be freely mobile
- Extravesical technique
  - Lich-Gregoir
    - bladder left intact: less bladder spasm, hematuria, less invasive
- Combined techniques
- Endoscopic techniques: not as good as open (70% success w/ single injection)
  - Nonautologous
    - Teflon
      - ◆ concern re: particles phagocytosed, seen in lung, brain, LN
    - Collagen
      - ◆ success of 60-65% 3mo after 1 injection
      - ◆ volume decreases w/ time, need for retreatment
    - Silicone microimplants
      - ◆ particle migration to distant organs
    - Deflux (dextranomer microspheres w/ hyaluronic acid)
      - ◆ induce fibroblast and collagen deposition
    - Detachable membranes
  - Autologous
    - Alginate and chondrocytes
- Laparoscopic techniques
  - modified Lich-Gregoir

## Chapter 59 Questions - VUR.doc

### What are the results for endoscopic therapy of VUR?

- 1<sup>st</sup> injection: 72%, regardless of material
- 2<sup>nd</sup> injection: 68%
- 3<sup>rd</sup> injection: 34%
- duplex vs. single system: 50% vs. 73%
- neurogenic bladder vs. normal: 62% vs. 74%
- child vs. adult: 73% vs. 65% (not significant)
- previous reimplant: 65%
- risk of recurrent VUR: 9%

### What is the risk of obstruction/dilation > 1mo after endoscopic tx?

- 0.2% - 50% require intervention

### What is the risk of UTI after injection?

- 6.4%
- febrile UTI: 0.75%
- cystitis: 6%

### Describe the Politano-Leadbetter method of VUR correction.

- transverse skin incision 2 fingerbreadths above symphysis pubis
- anterior rectus fascia opened
  - flaps developed superiorly and inferiorly above muscles
  - rectus and pyrimidalis muscles separated in midline
  - transversalis fascia and peritoneum swept from the dome of the bladder
- bladder opened in midline
  - inferior and lateral edges sutured to anterior rectus fascia
  - multiple moist sponges placed in dome of bladder to elevate bladder floor
  - trigone flattened and tense
- ureteral dissection performed w/ minimal tissue handling
  - 5-0 chromic suture placed above and below orifice
  - place feeding tube to aid ureteral dissection
  - mucosal cuff outlined w/ needle-tip cautery
  - place snap under ureter to find plane for ureteral dissection
  - sharp dissection parallel to ureter w/ tenotomy scissors
  - excise diseased ureter as needed
- sweep peritoneum from posterior bladder wall
  - visualize vas and sweep away
- pass Lauer from inside bladder through hiatus to location of neo-orifice
  - 2-2.5 cm superomedial from old hiatus
  - mucosa and muscle sharply incised
  - pass 2<sup>nd</sup> Lauer outside bladder by 1<sup>st</sup> clamp, guiding ureter through new hiatus into bladder
  - pass infant feeding tube to r/o obstruction
  - mucosa surrounding old hiatus mobilized and its musculature is closed
- develop submucosal tunnel to new hiatus w/ tenotomy scissors
  - Lauer delivers ureter through submucosal tunnel to its previous hiatus
  - distal ureter sutured w/ 5-0 chromic
  - no spatulation needed
- ureteral advancement if need more length
  - incise mucosa inferiorly, advancing ureter towards BN
- close bladder in 2 layers
- leave Foley

### Describe the Cohen cross-trigonal technique of VUR correction.

- transverse skin incision, bladder opened as per P-L correction
- mobilization of ureters
  - avoid excessive dissection of trigone
- submucosal tunnel created w/ new mucosal hiatus just above the contralateral UO
  - if both ureters reimplanted, other tunnel developed so new UO just below contralateral UO
- suture ureters

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### Describe the Glenn-Anderson technique of VUR correction.

- initial exposure as per P-L correction
- intravesical ureter is mobilized to give 2-3 cm of ureteral length
- submucosal tunnel can be created w/ tenotomy scissors medially to original UO
  - may be simpler to incise mucosa to BN and raise flaps
- widened hiatus reapproximated w/ 3-0 Vicryl and ureter repositioned inferiorly near BN
  - if ureteral mobilization inadequate, muscular hiatus extended superolaterally by cutting detrusor and mobilizing peritoneum and other structures posterior to bladder

### Describe the Gil-Vernet technique of VUR correction.

- initial exposure as per P-L correction
- medially placed traction sutures near UOs
  - if ureters can be lifted from their beds to meet in the midline, they are candidates for this technique
- single transverse incision made through mucosa that joins both traction sutures
- 2 4-0 mattress sutures placed through intrinsic ureteral musculature and approximate the ureter to midline detrusor
- close mucosa vertically w/ fine chromics

### What are the RF for retention after Lich-Gregoir reimplantation?

- < 3 yrs
- boys
- pts w/ high grade VUR
- hx voiding dysfunction

### Describe the Lich-Gregoir technique of VUR correction.

- bladder filled
- initial exposure as per P-L correction
- bladder left intact and retracted medially
- obliterated hypogastric artery identified and ligated
- ureter isolated w/ vessel loop
- serosal and muscular layer of the detrusor opened along a straight course cephalad and lateral to UVJ
- 4-5cm length of detrusor cleared to create a trough
  - may be incised proximally and distally
- ureter placed within trough, closed over w/ 3-0
- Penrose left

### What are the complications of ureteral reimplantation?

- Early
  - VUR
    - due to trigonal edema
    - usually low grade and transient: treat conservatively
  - obstruction
    - due to edema, bleeding, bladder spasms, mucus plugs, clots
    - tx: NT or stent if does not resolve
- Late
  - VUR
    - failure to achieve sufficient submucosal length or failure to provide adequate muscular backing: most common cause
    - failure to tailor dilated ureter
    - failure to identify and treat secondary causes of VUR: neuropathic bladder, voiding dysfunction
    - tx: intravesical reimplantation, mucosa of old tunnel incised and scars sharply removed
  - obstruction
    - due to ischemia, angulation at hiatus, inadvertent passage through peritoneum or viscera
    - revise if chronic: intravesical reimplantation, peritoneum opened

### Describe the laparoscopic technique of VUR correction.

- Veress needle placed beneath umbilicus, obtain pneumoperitoneum at 15mmHg
- 2 trocars placed:
  - 1 in side opposite refluxing ureter, at MCL 1cm above umbilicus
  - 1 in infraumbilical midline for camera

## Chapter 59 Questions - VUR.doc

- 2 trocars positioned in L and R MCL, 2 cm above ASIS
- identify and transect obliterated umbilical
- bladder shifted away from operative side by grasping and retracting its dome
- mobilize 4cm of ureter proximal to UVJ to permit placement w/i bladder trough
- bladder trough created by incising detrusor w/ cautery
- ureter placed within trough, which is closed

### What is the definition of a megaureter (MGU)?

- ureter wider than 7mm
  - normal ureteral diameter rarely > 5mm
- can be applied to any big ureter

### How can one classify megaureters?

- Refluxing, non-obstructed
  - primary: lateral ureteral ectopia, prune-belly
  - secondary: BOO, voiding dysfunction
- Obstructed, non-refluxing
  - primary: aperistaltic juxtavesical segment 3-4cm long, unable to propagate urine, congenital stricture, ureteral valves
    - histologic abnormalities: disorientation of muscle, muscular hypoplasia/hypertrophy, mural fibrosis
    - results in functional obstruction
  - secondary
    - PUV
    - voiding dysfunction (neurogenic, Hinman's)
    - ureterocele
    - ectopic ureter
    - bladder diverticula
    - periureteral postreimplant fibrosis
    - external compression from retroperitoneal tumours
    - aberrant vessels
- Refluxing and obstructed
  - due to dysgenetic distal segment: does not coapt within intramural tunnel, results in ineffective peristalsis
- Non-refluxing, non-obstructed
  - primary
    - dx of exclusion → most newborn MGUs
    - may be due to a highly compliant ureter, increased urine output, transient urethral obstruction
  - secondary
    - UTI (endotoxin)
    - polyuria/DM/DI
    - sickle cell nephropathy
    - psychogenic polydipsia
    - Li toxicity
    - prune-belly

### What is involved in the evaluation of the child w/ megaureter?

- US
  - usually distinguishes MGU from UPJO
- VCUG
  - r/o VUR
  - assess quality of bladder
- diuretic renogram
  - MAG3 or DTPA to assess function/obstruction
  - defer for 3 mo to allow for glomerular maturation (blunted response to diuretics early)
- Whitaker test
  - may be needed w/ bilateral MGU (no reference)

### What is the treatment for MGU?

- Refluxing, non-obstructed
  - primary
    - medical management for infants, continued if trend towards improvement seen
    - surgery for older kids w/ persistent high-grade reflux

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- secondary
  - treat secondary cause
- Refluxing and obstructed
- Non-obstructed, non-refluxing
  - primary
    - medical management as long as renal function is not affected as UTIs not a problem
    - US q3-6mo
    - surgical correction if severe b/w age 1-2 if no improvement w/ severe hydro
  - secondary
    - treat secondary cause
- Antenatal MGU
  - observe: most will resolve

### What are the different ways to repair MGUs?

- Plication or infolding techniques
  - Starr plication
    - ureteral redundancy defined by applying clamps
    - ureter plicated anteriorly w/ interrupted 6-0 placed in Lembert fashion
  - Kalicinski plication
    - ureter divided longitudinally into 2 lumens
    - running suture woven through MGU
    - redundant ureter folded over, tacked together w/ interrupted sutures
- Excisional techniques
  - Hendren tapering
    - Allis clamps placed laterally
    - excessive ureter excised
    - running, locking 6-0 sutures used to reapproximate proximal 2/3 of ureter

### What are the indications for the different ways to repair MGUs?

- Plication or infolding techniques
  - useful for moderately dilated ureter
    - increased complications if plicate ureter > 1.75cm in diameter
  - preserves vascularity
- Excisional techniques
  - useful for severely dilated or thickened ureter

### What is the treatment for the dilated duplex ureter?

- Uretero-ureterostomy
- ureteropyelostomy
- common sheath reimplantation
- heminephrectomy and megaureter excision





## **Chapter 60**

### **• Prune-Belly Syndrome •**

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#### **What is the prune-belly syndrome?**

- congenital absence, deficiency, or hypoplasia of the abdominal musculature associated with:
  - large hypotonic bladder
  - dilated and tortuous ureters
  - bilateral cryptorchidism

#### **What are the other names for prune-belly?**

- triad syndrome
- Eagle-Barrett syndrome

#### **Describe the epidemiology of prune-belly.**

- 1 in 35,000-50,000
- increased risk in twins, blacks, children born to younger mothers
- fully developed syndrome almost exclusively in boys

#### **What is the cause of prune-belly?**

- unknown
  - obstruction of the posterior urethra
    - abdominal wall defect due to urinary tract distension or fetal ascites
    - testicular descent blocked by distended bladder
  - prostatic dysgenesis and fetal ascites are key factors
  - primary mesodermal error may cause both abdominal wall defect and GU abnormalities
    - both arise from paraxial intermediate and lateral plate mesoderm
- no genetic etiology

#### **What anomalies are associated w/ prune-belly?**

- GU
  - Kidney
    - renal dysplasia: > 50%
      - ◆ may be asymmetric
      - ◆ more severe in pts w/ urethral stenosis, megalourethra, or imperforate anus
    - hydronephrosis
    - UPJO
    - infection = greatest threat to renal parenchyma
  - Ureter
    - tortuosity and segments of massive distension alternating w/ segments of N/stenotic ureter
      - ◆ proximal ureter more normal
      - ◆ decreased # of smooth muscle cells, less capable of contraction
  - Bladder and Urachus
    - ureters enter bladder in lateral and posterior position
    - elongated interureteric ridge
    - VUR: up to 85%
    - replacement of bladder smooth muscle w/ connective tissue
    - large capacity bladder w/ reduced contractility
      - ◆ 50% can void spontaneously
    - delayed sensation to void
    - urachal diverticulum
  - Prostate/SV
    - wide BN, grossly dilated prostatic urethra from prostatic hypoplasia
    - narrow membranous urethra
    - decreased muscular fibers



## Chapter 60 Questions - Prune-belly.doc Syndrome

- rudimentary/absent SV
- atretic vas
- Urethra
  - congenital megalourethra: dilation of the anterior urethra w/o distal obstruction
    - ◆ scaphoid variety: maldevelopment of the spongiosum, causing urethral dilation w/ preservation of cavernosae and glans
    - ◆ fusiform variety: maldevelopment of spongiosum and cavernosae → entire phallus dilates
  - urethral atresia: poor prognosis
  - normal anterior urethra and penis
- Testis
  - bilateral cryptorchidism
    - ◆ intra-abdominal testes
  - decreased # of spermatogonia
  - Leydig cell hypoplasia
  - normal erection and orgasm w/ infertility
- Orthopedic (40-63%)
  - abdominal wall defect
    - abdominal wall muscles absent/deficient, but upper rectus and outer obliques are developed
      - ◆ nonspecific myopathology: variation in muscle fiber diameter and atrophic fibers
    - lax and redundant abdominal wall w/ bulging flanks
    - interferes w/ effective cough: increased risk of URTI
  - dimple on outer aspect of knee: most common
  - chest wall deformity: pectus excavatum/carinatum
  - scoliosis
  - sacral agenesis
  - congenital hip dislocation
  - genu valgum
  - talipes equinovarus
  - severe leg maldevelopment
- Pulmonary (55%)
  - pulmonary hypoplasia
  - lobar atelectasis
  - pneumothorax
  - pneumomediastinum
  - chronic/recurrent bronchitis/pneumonia: inability to generate effective cough
- Cardiac (10%)
  - patent DA
  - VSD
  - ASD
  - Tetralogy of Fallot
- GI
  - volvulus
  - intestinal malrotation: due to universal mesentery w/ unattached cecum
  - omphalocele
  - gastroschisis
  - Hirschsprung's disease
  - imperforate anus: more likely in association w/ urethral atresia and renal dysplasia
  - constipation: due to deficiency of abdominal musculature
    - may lead to acquired megacolon
  - HPB abnormalities
- Misc
  - splenic torsion
  - adrenal cystic dysplasia

### How can one classify prune-belly?

- Class I → fate cannot be altered
  - oligohydramnios, pulmonary hypoplasia, or pneumothorax
    - may not live beyond 1<sup>st</sup> few days of life due to severe oligohydramnios
  - +/- urethral obstruction or patent urachus
- Class II

## Chapter 60 Questions - Prune-belly.doc Syndrome

- typical external features and uropathy, but no immediate problems w/ survival
- +/- mild/unilateral renal dysplasia
- may develop urosepsis or gradual renal failure
- Class III → unlikely to require intervention
  - mild external features or incomplete
  - less severe uropathy, stable renal function

### What is the presentation of prune-belly?

- Prenatal
  - seen on US: difficult to distinguish from VUR or PUV
- Neonatal
  - considerable variability: see above
- Childhood
  - nadir Cr during infancy useful predictor of long-term renal function
    - if Cr < 60, renal fn stabilizes unless pyelo occurs
  - need circ + antibiotics
  - transplant in renal failure pts
- Adult
  - sx of renal failure + htn

### What is involved in the management of pts w/ prune-belly?

- Initial evaluation
  - stabilize cardiopulmonary function
  - Px and US
  - avoid VCUG unless results needed for immediate decision making
    - difficult to eradicate UTI once present
  - stable class II infant: serial Cr, lytes, cultures, US, DMSA scan, Whitaker test
- Medical management
  - exclude obstruction and VUR
  - antibiotic prophylaxis
- Surgical management
  - controversial
    - avoid reconstruction until after 3 months old to allow for pulmonary maturation
  - temporary diversion
    - vesicostomy in pts w/ intractable UTI or worsening renal function
    - cutaneous pyelostomy: only in pts w/ UPJO or UVJO or pts w/ unremitting infection
    - avoid proximal ureterostomy: jeopardizes ureter than can be used for reconstruction
  - ureteral reconstruction
    - ureteral tapering
  - reduction cystoplasty
    - remove wide urachal diverticulum
      - ◆ reshaping bladder into sphere does not improve emptying over time, and excessive bladder volumes recur
  - VIU
    - indicated in the rare pt w/ true anatomic urethral obstruction + UDS evidence of obstruction on PFS
  - repair of megalourethra
    - indicated in child w/ grossly dilated anterior urethra
      - ◆ deglove penile skin, excise redundant urethral wall, reconstruct over catheter
  - orchidopexy
  - abdominal wall reconstruction
    - improvement in cosmesis, improvement of bladder, bowel, and pulmonary function
    - external support devices used instead as well

### What are the options for orchidopexy in the pt w/ prune-belly?

- early transabdominal orchidopexy
  - complete transabdominal mobilization of cord
    - in pts up to 6mo
  - may be completed at time of ureteral reconstruction, or delayed until lung maturity
- Fowler-Stephens
  - preservation of peritoneum over the vas: important for protection of collateral vessels
  - staged vs. 1-stage: increased collateral circulation b/w vasal and distal testicular arteries → wait 6mo

## Chapter 60 Questions - Prune-belly.doc Syndrome

- microvascular autotransplantation
  - microvascular anast b/w gonadal vessels to inferior epigastric

### What are the options for abdominal wall reconstruction in the pt w/ prune-belly?

- Randolph technique
  - full thickness removal of abnormal region
  - transverse incision from tip of 12<sup>th</sup> rib to pubis and back to contralateral 12<sup>th</sup> rib
  - redundant skin excised, and healthy fascia reapproximated to ASIS and pubis
- Ehrlich technique
  - midline incision w/ elevation of skin and subcutaneous tissue
  - double-breasted overlapping advancement of each side towards the contralateral flank
  - preservation of the umbilicus requires mobilization on a vascular pedicle using inferior epigastrics
- Monfort technique
  - vertically oriented elliptical incision to isolate the redundant skin, which is elevated from underlying fascia and excised
  - circumscribe umbilicus and leave alone
  - enter abdominal cavity lateral to rectus, avoiding epigastrics
  - advance lateral fascia over central plate to increase wall thickness



## Chapter 61

### • **Exstrophy, Epispadias, and Other Bladder Anomalies** •

#### **What is the incidence of exstrophy?**

- 1 in 10,000-50,000
- risk of recurrence in given family 1 in 100
- risk of exstrophy in child of pts w/ exstrophy and epispadias is 1 in 70 → 500X increased incidence

#### **Describe the embryology of exstrophic bladder formation.**

- normally:
  - mesenchymal ingrowth b/w ectodermal and endodermal layers of cloacal membrane results in formation of lower abdominal muscles and pelvis
  - after ingrowth, urorectal septum grows caudally and divides cloaca into bladder anteriorly and rectum posteriorly
  - distally, septum reaches posterior remnant of bilaminar membrane, which perforates to form separate anal and urogenital openings
- exstrophy due to failure of cloacal membrane to be reinforced by ingrowth of mesoderm
  - premature rupture of cloacal membrane
  - ? overdevelopment of cloacal membrane, which prevents medial migration of mesenchymal tissue and proper lower abdominal wall development
  - ? abnormal development of the genital hillocks w/ fusion in midline below and not above cloacal membrane
  - ? abnormal caudal insertion of body stalk

#### **What anomalies are associated w/ exstrophy/epispadias?**

- Skeletal defects
  - bony abnormalities
    - external rotation of posterior bony segment by 12°
    - external rotation of anterior bony segment by 18°
    - pubic ramus shortening by 30%
      - ◆ pelvic diastasis
    - retroversion of acetabulum
    - increase in SI joint angle by 10°
    - more inferior rotation of pelvis
    - sacrum in exstrophy pts is 42% larger
  - all above deformities may be assymetric
  - leads to increased distance b/w hips, waddling gait
- Pelvic floor defects
  - puborectal slings support 2X more body weight than normal
  - levator ani positioned more posteriorly, more flattened
- Abdominal wall defect
  - triangular defect caused by premature rupture of the abdominal cloacal membrane
    - ◆ upper end of defect: umbilicus
    - ◆ lower end of defect: intrasymphyseal band → represents the divergent urogenital diaphragm
  - anterior sheath of rectus has a fan-like extension behind urethra and BN that inserts into intrasymphyseal band
  - distance b/w umbilicus and anus is shortened
  - inguinal hernia: 81% of M, 11% of F → often bilateral
- Anorectal defects
  - short broad perineum
  - anus directly behind urogenital diaphragm, displaced anteriorly → corresponds to posterior limit of triangular fascial defect
  - anal incontinence and rectal prolapse
    - due to divergent levator ani and puborectalis, distorted anatomy of EUS
    - **if rectal prolapse occurs after closure, need immediate cysto to r/o BOO**

## Chapter 61 Questions - Exstrophy.doc

- Genital defects
  - Male
    - anterior corporal length 50% shorter
    - posterior corporal length normal, w/ increased diameter
    - corporal bodies separate in parallel fashion
    - prostate normal weight, volume, but does not extend around urethra
      - ◆ urethra anterior to prostate
    - vas and ED normal
    - autonomic nerves displaced laterally
  - Female
    - short vagina, normal caliber
    - stenotic vaginal orifice, displaced anteriorly
    - bifid clitoris
    - labia, mons divergent
    - uterus enters vagina superiorly so cervix in anterior vaginal wall
    - normal tubes and ovaries
    - predisposition to uterine prolapse due to pelvic floor defect
- GU defects
  - Bladder
    - ectopic bowel mucosa or isolated bowel loop or hamartomatous polyp on bladder surface
    - normal density and affinity of muscarinic receptors
    - increase in collagen:smooth muscle ratio, increase in type III collagen
      - ◆ decreased ratio after successful closure
    - decreased number of myelinated nerves per field
    - if bladder small, fibrosed, inelastic, and covered in polyps → repair may be impossible
  - Ureters
    - abnormal course, enters bladder w/ no obliquity → **VUR in 100%**
      - ◆ reimplant may be necessary prior to BN reconstruction if ++ BOO after closure
  - Kidney: horseshoe, ectopic, hypoplastic, solitary all seen
  - pouch of Douglas: enlarged, ++ deep

### What variants of the exstrophy complex can exist?

- pseudoexstrophy
  - characteristic MSk defect, w/o major GU tract anomaly
  - low set umbilicus, divergent rectus that attach to separated pubic bones
- superior vesical fistula variant
  - MSk and skeletal defects identical, but persistent cloacal membrane ruptures only at uppermost portion
  - superior vesical fistula results → resembles vesicostomy
- duplicate exstrophy
  - superior vesical fistula opens, but there is later fusion of the abdominal wall
  - portion of bladder elements (mucosa) remains outside
  - variable external genital manifestations
- "covered exstrophy" aka split symphysis defect
  - MSk defect w/o significant GU tract anomaly
  - exstrophic bladder covered w/ skin

### What findings on prenatal US are suggestive of bladder exstrophy?

- absence of bladder filling
- low-set umbilicus
- widening pubic ramus
- diminutive genitalia
- lower abdominal mass that increases in size w/ pregnancy

### What are the stages of closure for exstrophy?

- bladder, abdominal wall, and posterior urethral closure w/ bilateral innominate and vertical iliac osteotomy
- epispadias repair: at 6-12mo after testosterone stimulation
  - some have advocated epispadias repair in newborn period
  - Gearhart: limit combined procedures to boys of older age (4-6mo)
- BN reconstruction and antireflux procedure: at 4-5yrs, when child ready to participate in voiding program

## Chapter 61 Questions - Exstrophy.doc

### What is the initial management of the newborn w/ exstrophy?

- umbilical cord tied w/ 2-0 silk
  - prevents umbilical clamp from traumatizing delicate mucosa on bladder
- bladder covered w/ non-adherent plastic wrap
  - when diaper changed, irrigate bladder plate and replace wrap
- parental reassurance
- cardiopulmonary and general physical assessment
- DMSA and US of kidneys in 1<sup>st</sup> few hrs of life
  - renal structure, function, and drainage
- determine suitability for immediate closure
  - may require EUA
  - small fibrotic bladder patch will likely dehisce → wait 4-6 mo for plate to grow

### What are the options for management of the child w/ small fibrotic bladder plate unsuitable for immediate closure?

- wait for bladder to grow for 4-6 mo
- excise bladder plate and do conduit
- place small bladder inside for later use as posterior urethra → Arap procedure
- bladder augment, reimplant, and outlet procedure w/ continent urinary stoma

### Describe the surgical technique for primary closure + osteotomy in an exstrophy pt.

- Osteotomy
  - Pre-op
    - pt in supine position
    - prep and drape lower body below costal margins
  - Procedure
    - pelvis opened and exposed from iliac wings inferiorly to pectineal tubercle and posteriorly to SI joints
    - Gigli saw used to create transverse innominate osteotomy exiting anteriorly at a pt 1/2 way b/w ASIS and AIIS
      - ◆ posterior ileum may be incised from anterior approach
    - osteotome used to make closing wedge osteotomy vertically and just lateral to SI joints
    - proximal posterior iliac cortex left intact, used as a hinge
    - 2 fixator pins placed in inferior osteotomized segment, and 2 placed in the wing of ileum superiorly
    - Xrays to confirm placement
    - pelvis closed w/ suture b/w 2 pubic rami
  - Post-op
    - Xrays 7-10d post-op
    - pt remains supine for 4 weeks, ex-fix on for 6 weeks
    - after callus formation seen, fixating device and pins removed
- Bladder, Posterior Urethra, and Abdominal Wall closure
  - Procedure
    - strip of mucosa 2cm wide, from distal trigone to below verumontanum in male and to vaginal orifice in female is outlined
    - plane established b/w rectus and bladder
    - umbilical vessels ligated and divided
    - peritoneum taken off dome of bladder
    - incise fibers b/w BN, posterior urethra, and pubis
      - ◆ excision across urethral plate using rotational flaps if urethral lengthening needed
    - penile lengthening achieved by exposing corpora cavernosa bilaterally and freeing corpora from attachments to suspensory ligaments on pubic rami
    - urogenital diaphragm detached from rami
    - mucosa and muscle of bladder and posterior urethra closed onto penis in midline anteriorly over 12-14F sound
      - ◆ buttress w/ 2<sup>nd</sup> layer of local tissue posteriorly
    - place SP Malecot
      - ◆ ureteric stents only, urethra is not stented
    - horizontal mattress sutures placed in pubis, tied w/ knot away from neourethra
    - approximate rectus fascia and close skin
  - Post-op
    - US, bladder outlet calibrated w/ urethral sound
    - continuous antibiotics after closure → all pts have VUR
    - PVR by clamping SP tube, remove SP at 4 weeks
    - US 3mo later, q6mo

## Chapter 61 Questions - Exstrophy.doc

- cysto/VCUG yearly

### What are the indications for osteotomy in the exstrophy pt?

- when bladder closure performed after 72hrs of age
- if pelvis is not malleable
- if pubis > 4cm apart at the time of initial EUA
- if any doubt exists if pt needs osteotomy
- cloacal exstrophy

### What are the complications of osteotomy?

- femoral nerve palsy
- delayed ileal union
- infection
- muscle weakness

### What are the mechanisms of recurrence of diastasis after osteotomy?

- early loosening of pins before osteotomy healing
- long-term undergrowth of ischiopubic segment

### What parameters predict success after closure of exstrophy?

- size of bladder template at birth
- successful primary closure w/ absence of infections

### What is the management of BOO after primary closure?

- urethral dilation
- CIC
- antireflux procedure
- bladder outlet revision
  - may be needed as early as 6-12mo if UTIs
  - prevents VUR and ureteral dilation
- if recurrent UTI + bladder distension, do cysto
  - r/o erosion of intrapubic stitch

### What are the components of penile reconstruction for epispadias?

- correction of dorsal chordee
  - lengthening of dorsomedial aspect of corpora by incision and anast of corpora themselves
  - placement of dermal graft
  - shortening or medial rotation of the ventral corpora
- urethral reconstruction
  - Young: tubularization of the dorsal urethral groove → high incidence of fistula
  - tubularization of urethral plate, moving plate under corporal bodies after closure to decrease fistula incidence
- glandular reconstruction
- penile skin closure
  - Z-plasty incision and closure at base of penis: prevents skin contraction
  - ventral foreskin split and brought to dorsum as lateral preputial flaps

### Describe the surgical technique of penile and urethral closure in exstrophy.

- Modified Cantwell-Ransley repair
  - traction stitch through glans
  - incisions made over 2 parallel lines marked previously on dorsum of penis that outline 18mm strip of urethral mucosa
    - extends from prostatic urethral meatus to tip of penis
  - deep vertical incision made in distal urethral plate
    - closed transversely w/ 6-0 (IPGAM procedure)
    - flattens distal urethral plate, advances urethra to penile tip
  - glandular mucosal areas of the dorsal glans are excised
  - lateral skin flaps are mobilized and undermined
  - Z-incision of suprapubic area permits wide exposure and division of suspensory ligaments
  - ventral penile skin taken down to scrotum

## Chapter 61 Questions - Exstrophy.doc

- preserve mesentery to urethral plate
- urethral plate dissected distally past level of junction of glans w/ corporal bodies
- separate penis into 3 components: 2 corpora and urethra
- no complete penile disassembly: leave 1cm attachment of mucosa plate to glans
- NVB left intact
- corporal bodies incised or rotated over urethra
- urethral strip is closed in a linear manner over 8F stent w/ 6-0
- incisions made in corporal bodies, closed over neourethra
- glans wings closed over glandular urethra w/ subQ 5-0
- glans epithelium closed w/ 6-0
- ventral skin brought up and sutured to ventral corona
- skin reapproximated w/ 5-0 or 6-0 interrupted
- Z plasty at penile base closed
- stent in urethra x 12d
- Female genitalia
  - reconstruct mons at time of initial closure
  - denude bifid clitoris medially, bring together in midline

### What are the results after modern staged functional closure of exstrophy?

- Initial closure
  - onset of eventual continence quicker and continence rates higher in those w/ successful initial closure
    - 70-90% chance of continence
  - 2 closures: 60% chance of adequate bladder capacity for BN reconstruction
  - 3 closures: 40% chance of adequate bladder capacity, 20% chance of continence
- Epispadias repair
  - modified Cantwell-Ransley repair: 23% fistula rate immediately, 19% at 3mo
  - fistulae usually occur at base of penis, where urethra comes up proximally b/w corporal bodies
- BN repair
  - 69% continence, higher in F
  - bladder capacity at time of BN reconstruction is an important determinant of success
  - continence more likely in pts that underwent closure < 72h of age, or >72h w/ osteotomy
    - pts that undergo primary closure > 72h w/o osteotomy have lower rate of continence (10%)
  - continence rates higher in those w/ bladder capacity > 85cc at time of BN repair
    - defer BN closure until capacity > 85cc, and child ready to participate in voiding program
  - daytime continence: takes 1 yrs after BN construction
  - nighttime continence: takes 2-3 yrs after BN construction
    - DDAVP may increase the # of dry nights

### What are the signs of neourethral stricture after exstrophy repair?

- UTI
- increased bladder volumes on US
- bladder stones
- prolonged dry intervals
- unexplained rectal prolapse

### What are the various presentations of failure after exstrophy repair?

- Failed closure
  - bladder dehiscence
  - bladder prolapse
  - neourethral stricture
- Failed BN repair
  - failure of urinary continence
- Failed urethral reconstruction
  - urethrocutaneous fistula formation

### Describe the fertility and sexual function of the exstrophy patient.

- occasional pregnancy or initiation of pregnancy have been reported
  - may require ART
  - major complication after pregnancy: cervical and uterine prolapse
- normal sexual function and libido



## Chapter 61 Questions - Exstrophy.doc

### What is the incidence of cloacal exstrophy?

- exceedingly rare: 1 in 200,000-400,000 live births

### What findings on prenatal US are suggestive of cloacal exstrophy?

- Major
  - nonvisualization of the bladder
  - large midline infraumbilical anterior wall defect
  - cystic anterior wall structure
  - omphalocele
  - myelomeningocele
- Minor
  - lower-extremity defects
  - renal anomalies
  - ascites
  - widened pubic arches
  - narrow thorax
  - hydrocephalus
  - single umbilical artery

### Describe the embryology of cloacal exstrophy.

- normally: urorectal septum divides cloaca into anterior UGS and posterior anorectal canal
  - cloacal membrane invaded by lateral mesodermal folds at 4 weeks
- if mesodermal invasion does not occur, infraumbilical cloacal membrane persists
  - poor abdominal wall development
  - cloacal membrane ruptures
- extensive cloacal membrane serves as wedge defect
  - prevents normal migration of mesoderm
  - cloacal exstrophy occurs if wedge effect occurs before formation of urorectal septum

### What is the typical configuration of cloacal exstrophy?

- exstrophy of foreshortened hindgut or cecum
  - mucosa bulges b/w exstrophied hemibladders
- orifice of terminal ileum, rudimentary tailgut, and single appendix seen on surface of everted cecum
- blind-ending tailgut
- ileum prolapsed
- pubis widened
- hips externally rotated and abducted
- phallus separated into R and L halves w/ adjacent labial or scrotal halves
  - innervation arises from pelvic plexus on anterior surface of rectum
  - nerves to hemibladders travel the midline along posteroinferior surface of rectum, extend laterally to hemibladders

### What anomalies are associated w/ cloacal exstrophy?

- spina bifida
- upper GU tract anomalies
  - renal ectopia
  - renal agenesis
  - hydro
  - MCDK
  - fusion anomalies
- Gyne
  - Mullerian anomalies: duplication of uterus and vagina most common (95%)
- MSk
  - club foot: most common
- GI
  - omphalocele: 88%
  - malrotation
  - duplication anomalies
  - anatomically short bowel
  - short gut syndrome

## Chapter 61 Questions - Exstrophy.doc

- CVS/Pulmonary: rare

### What is involved in the management of the pt w/ cloacal exstrophy?

- Initial management
  - medical stabilization
  - evaluation of associated anomalies
  - bowel moistened and covered
- Gender assignment
  - limited to genetic male pt w/ cloacal exstrophy: difficult if XY w/ minimal phallus
- Surgical reconstruction
  - Bladder closure: soon after initial assessment
    - One-stage
      - ◆ excision of omphalocele
        - ♦ keep hindgut for later use for bladder augment
      - ◆ separate cecal plate from bladder halves
      - ◆ joining and closure of bladder halves and urethroplasty
      - ◆ bilateral anterior innominate and vertical iliac osteotomy: in all kids
      - ◆ gonadectomy in males w/o phallus
      - ◆ terminal ileostomy/colostomy
      - ◆ genital revision
    - 2-stage
      - ◆ 1<sup>st</sup> stage
        - ♦ excise omphalocele
        - ♦ separate cecal plate from bladder halves
        - ♦ join bladder halves
        - ♦ gonadectomy if needed
        - ♦ terminal ileostomy
      - ◆ 2<sup>nd</sup> stage
        - ♦ close joined bladder halves and urethroplasty
        - ♦ bilateral anterior innominate and vertical iliac osteotomy
        - ♦ genital revision
  - Anti-incontinence/reflux procedure: age 4-5yrs
    - bladder capacity > 85cc
    - more difficult in M pts that undergo sex reassignment
    - options: orthotopic urethra, catheterizable stoma, bladder augment
  - Vaginal reconstruction
    - use colon, ileum, skin graft

### What is the incidence of epispadias?

- Male
  - 1 in 117,000
  - 70% complete epispadias w/ incontinence
- Female
  - 1 in 484,000

### How can one classify female epispadias?

- least severe
  - urethral orifice appears patulous
- intermediate
  - urethra dorsally split along most of the urethra
- most severe
  - urethral cleft involves entire length of the urethra and sphincter: pt incontinent

Describe the embryologic formation of epispadias.

- defective migration of the primordium of the genital tubercles

### What is the typical configuration of epispadias?

- Male
  - virtually identical to defect seen in exstrophy
    - defect in dorsal wall of urethra

## Chapter 61 Questions - Exstrophy.doc

- normal urethra replaced w/ broad mucosal strip lining the dorsum of the penis toward the bladder
- sphincteric incompetence
- displaced meatus is free of penile deformity
  - ◆ may be found on glans, shaft, or penopubic region
- all male epispadias have dorsal chordee
- wide symphysis
- Female
  - urethral cleft
  - bifid clitoris
  - depressed mons
  - poorly developed labia
  - normal vagina and internal genitalia

### What anomalies are associated w/ epispadias?

- Male
  - usually confined to deformities of external genitalia, diastasis of the pubis, and incontinence
    - renal agenesis
    - VUR: 30-40%
- Female
  - VUR: deficient UVJ

### What is the surgical management of epispadias?

- Male
  - release of dorsal chordee
  - division of suspensory ligaments
  - dissection of the corpora from their attachments to the inferior pubic ramus
  - lengthening of the urethral groove
  - lengthening of the corpora
  - urethral reconstruction
    - transverse island flap
    - complete penile disassembly
    - modified Cantwell-Ransley technique
- Female
  - pt in lithotomy
  - excise glabrous skin over mons
  - urethral incision at cephalad extent of vertical incision at base of mons
  - inverting closure of urethra over 10-12F Foley
  - denude medial ½ of clitoris and labia
  - fat from mons used to cover suture line and obliterate prepubic space
  - clitoris and labia brought together
  - close subQ layer w/ 4-0

### What are the results after surgical reconstruction of epispadias?

- 87% continence
  - time interval of 18mo

### What is the cause of bladder agenesis?

- unknown
  - atrophy of anterior division of cloaca

### What is the typical configuration of the ureters w/ bladder agenesis?

- UO may terminate in uterus, vaginal wall, vestibule, rectum
- often associated w/ severe anomalies
  - neuro, ortho, GU (solitary kidney, renal agenesis/dysplasia, absence of prostate, SV, penis)
- small bladder may be dysplastic or hypoplastic

### What is the typical location for congenital bladder diverticulum?

- lateral and cephalad to UO
  - may incorporate the ureteral tunnel, and ureter may drain into diverticulum
  - causes VUR

## Chapter 61 Questions - Exstrophy.doc

### What is the etiology of congenital bladder diverticulae?

- inherent weakness of the detrusor
  - deficiencies of fascial sheath

### What syndromes are associated w/ congenital bladder diverticulae?

- Ehlers-Danlos
- Menkes'
  - neurodegenerative and CT disorder, increases in tissue copper content and metallothionein
- Williams'
  - mental retardation, facial anomalies, aortic stenosis
- Prune belly

### What are the indications for surgical intervention of bladder diverticulae?

- recurring UTI
- persistent VUR
- BOO
- significant ureteral obstruction

### What is congenital megacystis?

- entity in which the bladder is associated w/ massively refluxing megaureters
- normal bladder contractility
  - recycling of urine into upper tracts leads to increase in bladder capacity
- may be associated w/ Ehlers-Danlos, BOO, or microcolon intestinal hyperperistalsis syndrome
- tx: correct VUR
  - reduction in bladder size usually not needed

### What are the different tissue layers of the urachus?

- epithelial canal w/ cuboidal or transitional epithelium
- submucosal CT layer
- outer layer of smooth muscle: thickest near bladder

### What is the embryologic origin of the urachus?

- allantois is an extraembryonic cavity located within the body stalk that projects onto the anterior surface of the cloaca

### What are the different patterns of urachus obliteration?

- Type I: urachus fails to retain its attachment to bladder dome separate from each umbilical artery
- Type II: urachus fuses w/ one of the umbilical arteries and continues as a single fibrous cord to the umbilicus
- Type III: urachus fuses w/ both the umbilical arteries and continues as a single structure w/ umbilicus
- Type IV: urachus terminates before fusing w/ umbilical arteries, ending within the fascia or blending into a band of fibrous tissue

### What are the different forms of patent urachus?

- persistent patent urachus
  - failure of obliteration of urachal remnant
- vesicoumbilical fistula
  - represents failure of the bladder to descend

### What are the sx of patent urachus?

- local cord enlarged and edematous
- delay of normal slough of cord

### What is the most common organism found in an infected urachal cyst?

- *S. aureus*

### What are the complications of an infected urachal cyst?

- rupture of the preperitoneal tissues
- rupture into the peritoneal cavity → peritonitis
- inflammatory involvement of the adjacent bowel and formation of enterocutaneous fistula

## **Chapter 61 Questions - Exstrophy.doc**

### **What is the usual location of a urachal cyst?**

- usually in distal 1/3 of the urachus  
→ may occur in proximal 1/3

### **What are the sx of an infected urachal cyst?**

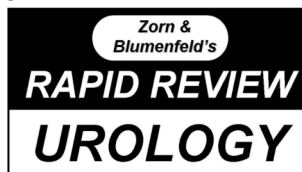
- lower abdo pain
- fever
- voiding sx
- midline hypogastric tenderness
- palpable mass
- evidence of UTI

### **What is the tx of an infected urachal cyst?**

- I&D of infected cyst
- excision after inflammation subsides

### **What is the tx for patent urachus?**

- excision of all anomalous tissue in bladder
  - infants: small curved subumbilical incision
    - bladder dome is still high and accessible
  - older kids: transverse midhypogastric incision



## Chapter 62

# **•Surgical Technique for One-Stage Reconstruction of the Exstrophy/Epispadias Complex•**

**What is involved in the disassembly technique with complete primary exstrophy repair (CPR)?**

- Pre-op
  - ligation of umbilical cord w/ silk suture
  - cover exposed bladder w/ plastic wrap
  - bladder irrigated w/ NS w/ each diaper change
  - IV antibiotics preop
  - US to assess kidneys
  - spinal US to rule out spina bifida
  - avoid NO as anaesthesia: causes bowel distension
  - NG
- Procedure
  - Initial dissection
    - standard prep
    - 3.5F umbilical artery catheters into both ureters, suture into place w/ 5-0 chromic
    - separate bladder plate from adjacent skin and fascia w/ fine-tip (Colorado) cautery
    - umbilical vessels are ligated
  - Penile-Urethral dissection
    - traction sutures into each hemiglans
      - ◆ placed transversely initially, and rotated to parallel vertical orientation as corpora rotate medially
    - circumcising incision
    - develop initial plane of dissection above Buck's fascia ventrally
    - as dissection progresses medially, dissect above tunica albuginea
    - lateral dissection of penile shaft skin and dartos fascia from corporal bodies
      - ◆ **lateral dissection always superficial to Buck's fascia, as NVB located laterally in epispadiac penis**
  - Complete penile disassembly
    - penis disassembled into 3 components: R and L corpora, and urethral wedge
    - provide exposure to intrasymphyseal band and allow adequate proximal dissection
    - establish plane b/w urethral wedge and corpora
    - keep spongiosum w/ urethral plate: same blood supply
    - cannot use paraexstrophy skin flaps: will devascularize distal urethra
  - Proximal dissection
    - deep incision of intersymphyseal ligaments posterior and lateral to each side of the urethral wedge
      - ◆ allows bladder to achieve posterior position in the pelvis
    - dissection carried out until pelvic floor musculature is visible
  - Primary closure
    - SP tube placed
    - primary closure of bladder w/ 3 layer closure w/ Monocryl and Vicryl
    - urethra tubularized w/ 2-layers of Monocryl
    - tubularized urethra placed ventral to corpora
    - reapproximate pubic symphysis w/ 2-0
      - ◆ leave knots anterior to prevent erosion into BN
    - reapproximate rectus w/ 2-0
    - reconfigure penile skin w/ primary dorsal closure or Byars flaps
    - rotate corporal bodies medially, reapproximated w/ fine interrupted sutures
    - urethra brought up to each hemiglans ventrally to create an orthotopic meatus
    - reapproximate glans epithelium, glans tissue reduction
- Post-op

## **Chapter 62 Questions - Exstrophy OR.doc**

- pt immobilized to decrease lateral stresses on closure
  - use spica cast x 3 weeks to prevent external hip rotation

### **What post-op factors directly affect success of initial closure?**

- postop immobilization
- postop antibiotics
- ureteral stents
- pain management
- avoid abdominal distension
- nutritional support
- secure fixation of urinary drainage catheters



## **Chapter 63**

### **• PUV and other anomalies •**

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**What is the most common GU cause for renal failure and transplantation in kids?**

- PUV

**How does one classify PUV?**

- Type 1: obstructing membrane that arises from the posterior and inferior edge of the veru, and radiates distally toward the membranous urethra
  - single membranous structure with the opening near veru
  - due to anomalous insertion of mesonephric ducts into primitive fetal cloaca
    - normally insert laterally onto cloaca, and migrate posteromedially and cranially
    - if insert too anteriorly, migration impeded by infolding cloaca and may fuse in midline anteriorly
  - kids w/ type I valves do not have plicae colliculae
- Type 2: originally described as folds radiating in cranial direction from veru to posterolateral bladder neck
  - do not exist
  - represent hypertrophy of the thin superficial muscle that runs from UO to opening of ED on veru
- Type 3: incomplete dissolution of urogenital membrane
  - discrete ringlike membrane w/ central aperture
  - distal to veru at level of membranous urethra
  - worse prognosis, only 5% of valves
- (Type 4: seen with prune-belly → flabby unsupported prostate falls in on itself, causes BOO)

**How do PUV present?**

- sx are age dependent
- Newborn
  - abdo masses: distended bladder, hydro
  - ascites: more favourable prognosis
    - transudation of retroperitoneal urine across the thin and permeable peritoneum
    - may develop severe electrolyte abnormalities and life-threatening abnormal fluid shifts after birth
  - respiratory distress from pulmonary hypoplasia: most common cause of death from PUV
    - cyanotic, low Apgars, require intubation and resuscitation
  - oligohydramnios, Potter's, thick walled bladder
- Neonate (few weeks)
  - urosepsis, dehydration, lyte abn, poor stream
- Toddler
  - UTI, voiding dysfunction
  - better renal function
- School-age: least common age of presentation
  - voiding dysfunction: incontinence

**What is the youngest age that a child can have IHD?**

- no age restriction: must be > 3kg or so

**What are the causes of deteriorating renal function in a child with PUV?**

- renal parenchymal dysplasia
  - microcystic, develops most severely in peripheral cortical zone
  - due to maturation of the primitive metanephric blastema in the presence of high intraluminal pressures
- incomplete resection of valves
- parenchymal injury from infection or hypertension
  - kids are at risk of UTI due to VUR, ureteral stasis, incomplete emptying
- progressive glomerulosclerosis from hyperfiltration, diets high in protein



## **Chapter 63 Questions - PUV.doc**

### **What is the cause of renal dysplasia in PUV?**

- maturation of primitive metanephric blastema in presence of high intravesical pressures

### **What is the VURD syndrome?**

- Valves, Unilateral Reflux, Dysplasia  
→ presence of nonfunctioning kidney (dysplasia) with reflux in presence of valves

### **What is the most important parameter in kids w/ PUV in determining future renal function?**

- severity of the renal dysplasia

### **What anatomic conditions are associated with improved renal function in kids w/ PUV?**

- massive unilateral VUR
- large bladder diverticula
- urinary ascites

### **What are conditions associated w/ PUV?**

- VURD
- decreased renal tubular function
- hydronephrosis
- VUR
- bladder dysfunction
- cryptorchidism (10%)
- infertility
- prune belly

### **What is the effect of PUV on renal tubular function?**

- 50% of pts w/ valves will have significant impairment of urinary concentrating ability  
→ acquired form of nephrogenic DI, w/ fixed high urinary flow  
→ do not respond to ADH treatment, since DI due to tubular damage

### **What is the relevance of an infant with a fixed high urinary flow rate?**

- infants are prone to dehydration and lyte imbalance
- ureteral and vesical dysfunction  
→ if decreased bladder compliance, increased storage pressures are reached quickly

### **What are the causes of persistent hydro after valve ablation?**

- UVJ obstruction  
→ rare: need Whitaker study to assess if obstruction present
- faulty ureteral musculature
- high intravesical pressures
- high urinary flow rates
- insufficient waiting time  
→ may take years after primary valve ablation for final improvement in ureteral caliber

### **How often is VUR associated with PUV?**

- between 1/3 and 1/2 of these pts have VUR at initial diagnosis
- resolves spontaneously in 1/3 of pts after obstruction eliminated, persists w/o problems in 1/3, and 1/3 have problems requiring reimplantation

### **What is the cause of VUR associated w/ PUV?**

- high intravesical pressures
- paraureteral diverticulae
- loss of uretero-vesical valvular competence
- primary ureteral bud anomaly

### **What is the significance of VUR associated w/ PUV?**

- VUR w/ PUV associated w/ poorer prognosis  
→ bilateral reflux mortality rate 57%, unilateral VUR 17%, no VUR mortality 9%

### **What is the "valve bladder?"**

## Chapter 63 Questions - PUV.doc

- detrusor dysfunction in a patient w/ PUV
  - primary myogenic failure, uninhibited bladder activity, poor compliance
  - cause for detrusor dysfunction remains unclear
- patients w/ incontinence during childhood have more severe degrees of renal failure
  - bladder dysfunction may be a factor causing renal function to deteriorate
  - 50% of boys still damp during the day well into late childhood, but achieve dryness in majority of cases

### What is the treatment of vesical dysfunction in PUV kids?

- anticholinergics
- CIC, timed voiding
- augment

### Outline the management of a child w/ PUV.

- depends on degree of renal failure and the child's age
- all require RBUS and VCUG w/ follow-up
- older children
  - endoscopic destruction of valve
- very young infant
  - place small transurethral catheter: feeding tube
  - start antibiotics
  - IV fluid rehydration
  - assess renal function after 5-7 days of catheter drainage
    - normal/satisfactory renal function: endoscopic destruction of valves
      - ◆ if urethra too small: antegrade destruction of valves via SP tract, w/ laser, urethrotome, ureteroscope
      - ◆ vesicostomy if urethra too small to allow valve ablation
    - poor renal function after catheter drainage: **controversial**
      - ◆ options: valve ablation, vesicostomy, or supravescical diversion
  - after destruction of valves, follow Cr and hydro on US
  - VCUG at age 2/12

### Where and how does one incise PUV during ablation?

- single wire (not loop) used
- current high enough only to incise valve, not to cause diffuse thermal injury
- incise at 4, 8, 12 o'clock
- advance wire from membranous urethra into dilated prostatic urethra
- Crede maneuver after to ensure obstruction is resolved
- catheter x 1-2 days post-op

### Indications for supravescical diversion for PUV:

- controversial: commits child to major reconstruction later
  - severe urosepsis that doesn't resolve w/ antibiotics
  - very poor renal function after several days of catheter drainage

### What are the techniques one can use to perform high cutaneous ureterostomy?

- loop ureterostomy
- Sober ureterostomy: ureter transected, proximal end brought to skin, distal end anastomosed end-to-side to proximal
- ring ureterostomy: loop brought to skin, but anastomosis completed b/w proximal and distal end as well
  - Sober and ring ureterostomies allow some urine to reach the bladder for cycling

### Describe the Blocksom technique of cutaneous vesicostomy.

- small transverse incision made 1/2 way b/w pubis and umbilicus
- rectus fascia incised transversely, and rectus muscles divided in midline, exposing the bladder
- bladder mobilized superiorly using traction sutures
- peritoneum peeled off the dome, which is mobilized into the incision
- incision made into dome of bladder
- bladder wall sutured to fascia w/ interrupted sutures
- bladder edges sutured to skin w/ interrupted chromic or Dexon
- place stoma high on bladder (beyond the urachus) to minimize risk of vesical prolapse

### Characteristics of PUV on prenatal US:

## Chapter 63 Questions - PUV.doc

- bilateral hydro
- thickened bladder
- dilated prostatic urethra
- amniotic fluid abnormality

### Characteristics of renal dysplasia on prenatal US:

- dysplastic parenchyma is echodense compared to normal
- What are the pre- and post-natal prognostic variables that predict poor postnatal renal function?
- amniotic fluid volume: moderate to severely decreased
  - sonographic appearance of renal parenchyma: increased echogenicity to cystic
  - fetal urinary chemistries
    - Na > 100
    - Cl > 90
    - mOsm > 210
    - u/o < 2 cc/hr
    - beta-2 microglobulin

### What is the most objective finding that suggests that prenatal intervention should be considered in PUV?

- pt w/ normal amniotic fluid volume having serial US showing oligohydroamnios later on

### What is the prognosis for children w/ PUV?

- 2-3% death
- prognosis relates to nadir serum Cr

### What are the causes of congenital obstruction of the anterior urethra?

- anterior urethral valves: congenital urethral diverticulum that balloons and extends into urethral lumen → most common
  - during voiding, diverticulum expands, ballooning ventrally and distally beneath the thinned spongiosum
  - flaplike dorsal margin extends into the urethral lumen, obstructing flow
- valvular obstruction of the fossa
- cystic dilation of the ducts of Cowper's glands

### Where in the urethra are anterior valves seen?

- almost always seen in midline ventrally
  - have been described in equal incidence in every portion of anterior urethra

### Dx of anterior urethral valves:

- VCUG
- US

### What are potential etiologies of anterior valves?

- incomplete fusion of segment of urethral plate
- incomplete development of the corpus spongiosum with ballooning of the urethral mucosa due to inadequate support

### Management of anterior valves:

- similar to PUV
  - transurethral drainage
  - antibiotics
  - electrolyte management
  - valve ablation
    - endoscopic: engage distal margin of the valve and incise it in the midline
    - open resection and reconstruction: patch graft urethroplasty

### What is a syringocele?

- cystic dilation of the duct of Cowper's gland within the bulbous urethra

### What is a megalourethra?

- nonobstructive urethral dilation
- associated w/ abnormal development of the corpus spongiosum and abnormal development of the corpus cavernosum
- associated w/ other abnormalities of the GU system
- two types:

### Chapter 63 Questions - PUV.doc

- scaphoid: spongiosum is only abnormal segment
- fusiform: associated w/ defects in cavernosa
- variant: megameatus intact prepuce (MIP)
  - coronally positioned, wide-mouthed meatus and fully formed foreskin

### What abnormality is associated w/ megalourethra?

- prune belly

### Outline the management of the megalourethra.

- cosmetic if upper tracts are normal
  - trim urethra for normal caliber

### How are urethral duplications classified?

- dorsal
  - accessory meatus lies above glandular meatus
  - normal meatus is the **ventral** meatus, in regular position on the glans
  - dorsal meatus is often blind ending
    - often incontinent if reaches bladder
  - may be related to exstrophy-epispadias complex: may have widened symphysis
- ventral
  - may be complete, with 2 separate urethras coming off the bladder
  - most serious variation is if ventral urethra meets anal margin
    - urine preferentially goes posteriorly to anal margin
  - dorsal urethra often atretic and is not used in formal repair
    - if dorsal urethra is catheterizable, gentle gradual dilation may allow for use (PADUA procedure – Progressive Augmentation by Dilating the Urethra Anterior)

### What are prostatic urethral polyps?

- benign lesions that represent developmental error in invagination process of submucous glandular material of the inner zone of the prostate
- almost always in prostatic fossa

### How do prostatic urethral polyps present?

- hematuria, obstructive sx, strangury





## **Chapter 64**

### **• Voiding Dysfunction in Children: Neurogenic and Non-Neurogenic •**

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#### **What is involved in a urodynamic evaluation of a child?**

- Consent
  - explanation of test
  - booklet
  - attempt to minimize anxiety
  - instruct child to come w/ full bladder
- History
  - mother's pregnancy history
  - child's birth and development
  - bowel and bladder habits
  - note time of child's previous urination
- Premedication (if needed)
  - EMLA
- UDS
  - inject small amount of Xylojet
  - catheterized w/ 7F or 11F triple-lumen UDS catheter
    - measure Pves
    - bladder drained, PVR measured
  - pass rectal catheter
  - UPP
    - measures passive resistance of a particular point within the urethra to stretch
    - NS infused through catheter as it is withdrawn at a rate of 2mm/sec
  - sphincter EMG
    - 24G concentric needle electrode inserted perineally in boys, periurethrally in girls
      - ◆ advanced into skeletal muscle component of EUS
      - ◆ patch electrodes can be used
    - can measure intactness of sacral cord function by:
      - ◆ looking at waveform of motor unit AP
      - ◆ record response to BCR, anal stimulation, Crede, Valsalva
      - ◆ voluntary contraction of EUS
      - ◆ reaction of EUS to filling
  - filling CMG
    - fill slowly w/ warm NS
    - divert child by asking questions
  - child urinates to obtain voiding pressure
  - flowrate

#### **How is the rate of bladder filling selected for a UDS?**

- calculate child's predicted capacity
  - $> 2 \text{ yrs} = (\text{age}/2 + 6) \times 30\text{cc} = (\text{age} \times 15) + 180$
  - $< 2 \text{ yrs} = (2 \times \text{age} + 2) \times 30\text{cc} = (\text{age} \times 60) + 60$
- fill bladder w/ 10% of expected capacity / min
  - even slower if important to determine very mild degrees of hypertonicity

#### **What is the normal voiding pressure for children?**

- boys: 55-80cm water
- girls: 30-65cm water
- higher in infants

#### **What is the most common cause of neurogenic voiding dysfunction in children?**

*Rapid Review Urology –Study Notes (Kevin C. Zorn & Aaron Blumenfeld, 6/2006©)*

## **Chapter 64 Questions - Voiding dysfn.doc**

- myelodysplasia: abnormal development of the spinal canal and cord

### **What is the incidence and familial risk of myelodysplasia?**

- General population: 0.1%
- Mother w/ one child: 2-5%
- Mother w/ 2 children: 10%
- Pt w/ myelodysplasia: 4%
- Mother > 35yrs: 3%
- Sister of mother w/ affected child: 1%
- Sister of father w/ affected child: 0.3%
- Nephew who is affected: 0.2%

### **What anomalies encompass the spectrum of myelodysplasia?**

- meningocele = just the meninges but no neural elements extend beyond confines of vertebral canal
- myelomeningocele = neural tissue (nerve roots or portion of cord) evaginated with meningocele  
→ 90% of all open defects
- lipomyelomeningocele = fatty tissue developed with cord structures and both are protruding

### **In descending order of frequency, where do most spinal defects occur in myelodysplasia?**

- lumbosacral vertebrae > lumbar > sacral > thoracic > cervical

### **What associated malformation occurs in most pts w/ meningocele?**

- Arnold-Chiari malformation in 85%  
→ cerebellar tonsils herniate downward through foramen magnum, obstructing the 4<sup>th</sup> ventricle → require VP shunt

### **How does the bony defect relate to the neurologic lesion?**

- bony defect provides little to no clue as to neurologic level or lesion produced
- may differ from 1 to 3 levels in either direction
- may see various neurologic lesions
- pts w/ thoracic or upper lumbar meningoceles may have normal sacral cords w/ intact reflex arcs  
→ children w/ thoracic or cervical lesions more likely to have just a meningocele and no neural involvement

### **What drugs may affect lower urinary tract function in children?**

- Cholinergic: urecholine
- Anticholinergic: Pro-Banthine, Ditropan, Detrol, glycopyrrolate, hyoscamine
- Sympathomimetic: phenylpropanolamine, ephedrine, pseudoephedrine (all  $\alpha$  agonists)
- Sympatholytic: prazosin, phenoxybenzamine, propranolol (all adrenergic blockers)
- Smooth muscle relaxants: flavoxate (Urispas), dicyclomine
- TCA: imipramine

### **What is involved in the newborn assessment of a child w/ MMC?**

- neurologic exam of lower extremities
- CIC: if pt cannot void spontaneously or after Crede maneuver
- PVR: normal bladder capacity in newborn is 10-15cc, acceptable PVR is < 5cc
- urine C&S
- Cr
- US abdo, VCUG, renal scan
- UDS when safe to transport child to urodynamics suite

### **What UDS results are seen in children w/ MMC?**

- Contractions  
→ 57% have bladder contractions  
→ 43% have areflexic bladder
- Reflex arc by EMG  
→ intact arc w/ no LMN lesion: 40%  
→ partial denervation: 24%  
→ complete loss of sacral cord function: 36%
- DSD  
→ synergic: 19%  
→ DSD +/- hyperreflexia: 45%

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- complete denervation: 36%
- US
  - 10-15% have abnormal urinary tract on US when 1<sup>st</sup> evaluated

### How does outlet resistance affect renal outcome in pts w/ MMC?

- increased risk of urinary tract deterioration if outlet resistance > 40cm H<sub>2</sub>O (McGuire 1981)
- increased risk of deterioration if DSD present
  - within 1<sup>st</sup> 3 years, 71% of newborns w/ DSD have urinary tract deterioration on subsequent studies
  - only 17% synergic children, 23% of completely denervated children had deterioration

### How does one treat the pt w/ DSD?

- CIC in newborn period +/- anticholinergics if:
  - Pdet during filling > 40cm H<sub>2</sub>O
  - Pdet during voiding > 80-100cm H<sub>2</sub>O
- results in urinary tract deterioration in only 8-10%

### What is the pediatric dose of oxybutynin?

- 1mg / yr of age q12h (up to 5mg PO BID)

### How does one manage VUR in the pt w/ MMC?

- can treat w/ CIC or anticholinergics, depending on grade of VUR
  - Grade 1-3, empty spontaneously: antibiotic prophylaxis
  - Grade 4-5, or cannot empty bladder: antibiotics + CIC
  - hyperreflexia +/- hydro: antibiotics + CIC + anticholinergics
- avoid Crede maneuver in pts w/ VUR → increases VUR
- if VUR so severe that CIC + anticholinergics fail to improve drainage: vesicostomy

### What are the indications for reimplantation in children w/ VUR and MMC?

- recurrent UTI while on antibiotics
- persistent hydro while on CIC
- severe VUR w/ UPJ obstruction
- VUR that persists into puberty
- VUR in child that is undergoing surgery to increase bladder outlet resistance

### What is the surveillance protocol in pts w/ MMC?

- UDS yearly until child is 5 yrs old
- VCUG/RNC yearly if DSD or partial denervation
- PVR q4-6mo if no DSD
- IVP/US yearly
- MR spine: if suspect tethered cord

### What is the most potent anticholinergic drug available today?

- glycopyrrolate

### How can one treat urinary incontinence in pts w/ MMC?

- CIC + anticholinergic (oxybutynin)
- add 2<sup>nd</sup> anticholinergic: glycopyrrolate, tolterodine, hyoscamine
- poor urethral resistance: add  $\alpha$ -agonist (phenylpropanolamine)
- surgery: if all else fails
  - refractory hyperreflexia: bladder augmentation or autoaugmentation
  - poor BN/urethral resistance: BN reconstruction
    - Young-Dees or Leadbetter procedure
    - Kropp
    - Salle
    - sling
    - AUS
    - collagen injection
  - diversion +/- BN closure: for intractable urinary incontinence

### What segments of bowel should not be used in children w/ myelodysplasia?



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- ileocecal segment
  - aggravates bowel dysfunction that is often present

### What are the advantages and disadvantages of using a gastric segment for augment?

- Advantages
  - fewer intrinsic contractions
  - spherical reservoir most efficient way to store fluids
  - acid milieu
  - free of mucus
- Disadvantages
  - hyponatremic hypochloremic metabolic alkalosis
  - hematuria dysuria syndrome

### What is the sexual function in a pt w/ MMC?

- 72% M have erections
- 70-80% F able to be pregnant
- 17-40% M able to father children
- breast development 2y earlier in F w/ MMC
  - ? change in pituitary function in girls secondary to hydrocephalus

### What treatment options are available for constipation/fecal incontinence in children w/ MMC?

- regular and efficient bowel emptying
- diets
- suppositories
- enemas
- biofeedback
- electrostimulation
- antegrade continence enema (ACE procedure)

### What are the different types of occult spinal dysraphisms?

- lipomeningocele
- intradural lipoma
- diastatomyelia
- tight filum terminale
- dermoid cyst/sinus
- aberrant nerve roots
- anterior sacral meningocele
- cauda equina tumour

### What physical findings are associated w/ an occult spinal dysraphism?

- dimple, skin tag, hair tuft
  - no open vertebral canal
  - in > 90%, there is a cutaneous abnormality
- vascular malformation
- subcutaneous lipoma
- high arched foot
- hammer/claw digits
- decrease in strength/size of one leg
- gait abnormality
- abnormal lower urinary tract function: 40-90%
  - abnormal in 1/3 of babies < 18mo
  - difficulty w/ toilet training, incontinence after a period of dryness, recurrent UTI, fecal soiling
- neurologic exam
  - normal in the majority
  - if present, most likely abnormality is UMN lesion: detrusor hyperreflexia or hyperactive sacral reflexes
  - LMN w/ denervation or detrusor areflexia in only 10% of young children

### Why do pts w/ occult spinal dysraphism ultimately end up w/ neurologic defects?

- compression of cauda equina by expanding lipoma
- tension on cord by tethering
  - results in ischemic injury

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- fixation of split cord by bony spicule or fibrous band  
→ 58% deteriorate if observed for 2 yrs

### How should pts w/ occult spinal dysraphisms be managed?

- UDS in any child w/ questionable cutaneous or bony abnormality of the lower spine
- US spine if < 4-6months: spine is not ossified yet
- treat w/ laminectomy +/- detethering of cord

### What is the definition of sacral agenesis?

- absence of part or all of 2 or more lower vertebral bodies

### What disorders in the mother will place a newborn at risk for sacral agenesis?

- insulin-dependent diabetes: 1% risk
- sacral agenesis: 16% risk  
→ deletion of 7q36

### What are the findings in a pt w/ sacral agenesis?

- bimodal presentation  
→ ¾ detected in early infancy, rest discovered b/w 4-5 yrs
- Hx  
→ failed attempts at toilet training  
→ UTIs: in 75% eventually
- Px  
→ normal sensation, normal lower extremity function  
→ short low gluteal cleft  
→ flattened buttocks  
→ absence of vertebrae on palpation
- Ix  
→ lateral Xray of spine reveals sacral anomaly  
→ VCUG: VUR in 37%  
➤ more likely in pts w/ UMN lesion (75%) vs. LMN (40%)  
→ MRI spine: cutoff of conus at T12
- UDS  
→ UMN (35%)  
➤ hyperreflexia, exaggerated sacral reflexes  
➤ no control over sphincter function  
➤ DSD  
→ LMN (40%): no reflexes  
→ normal in 25%

### What is the natural history of sacral agenesis?

- stable injury, rarely shows signs of progression
- UTI in 75%
- VUR in 37%

### How should pts w/ sacral agenesis be managed?

- UDS + VCUG + US abdo
- anticholinergics if hyperreflexia
- CIC +  $\alpha$ -agonist if cannot empty bladder or stay dry

### How can one classify anorectal malformation and imperforate anus, and what are their relative incidences?

- Wingspread classification system  
→ High (36%)  
➤ Female: anorectal agenesis +/- prostatic fistula, rectal atresia  
➤ Male: anorectal agenesis +/- vaginal fistula  
→ Intermediate (14%)  
➤ Female: rectovestibular fistula, rectovaginal fistula, anal agenesis w/o fistula  
➤ Male: rectovestibular urethral fistula, anal agenesis w/o fistula  
→ Low (47%)  
➤ Female: anovestibular fistula, anocutaneous fistula, anal stenosis

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- Male: anocutaneous fistula, anal stenosis
- Cloacal malformation (1%)
- Rare malformation (<1%)

### What is the incidence of imperforate anus?

- 1 in 4000-5000 live births
- M:F 1.5:1
- F: tend to have low lesions
- M: tend to have high lesions

### What findings are associated w/ imperforate anus?

- GU
  - fistulous communication b/w lower GU tract and bowel
  - UTIs: 26-52%
  - renal agenesis: usually L-sided
  - VUR
- MSK
  - spinal bony anomalies: 30-45%
- Neuro (18-50%)
  - tethered cord
  - thickened or fatty filum terminale
  - lipoma
  - neurogenic bladder: frequent

### How does one evaluate and manage the child w/ imperforate anus?

- Px
  - perineum: ?fistulae
  - upper and lower extremities
  - bony spine and cord
- Ix
  - lateral abdo Xray
  - US abdo
  - VCUG
  - US spine in 1<sup>st</sup> 3mo
  - UDS: before pull-through procedure and after
- Treatment
  - divided colostomy: if rectal-urinary tract fistula
    - gas, meconium, or Gm-ve UTI
  - Peña procedure

### What are the indications for UDS in a child w/ imperforate anus?

- bony abnormality of the spine
- spinal cord defect
- signs of dysfunction on VCUG or RBUS

### What are the most common findings on UDS in the child w/ imperforate anus?

- UMN w/ uninhibited contractions +/- bladder-urethral sphincter dyssynergy

### What is cerebral palsy?

- nonprogressive brain injury occurring in the perinatal period
  - produces neuromuscular disability or specific sx complex
- usually due to perinatal infection (sepsis, encephalitis) or period of anoxia that affects CNS

### What are the RF for CP?

- prematurity
- respiratory distress/arrest/apnea
- traumatic birth
- congenital hydrocephalus
- placenta previa/abruption
- < 2kg at birth

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- intraventricular hemorrhage
- cyanosis at birth
- mechanical ventilation postnatally
- neonatal seizure
- maternal UTI: increases risk 4-5X

### What are the sx of CP?

- delayed gross motor development
- abnormal fine motor performance
- altered muscle tone
- abnormal stress gait
- exaggerated DTRs
- continence: usually normal, achieved at later age

### What are the UDS findings in kids w/ CP?

- UMN lesion: 86%
- mixed upper and lower motor neuron lesion: 10%
- incomplete LMN lesion: 1.5%
- normal: 3%

### How does one manage UI in the child w/ CP?

- UDS
- anticholinergics
  - abolish uninhibited contractions
- monitor PVRs closely
  - CIC if not able to empty bladder

### How do SCI in children differ from those in adults?

- horizontal vs. vertical orientation of facets in vertebral bodies predisposes to AP subluxation in children
- delayed supportive effect of paraspinal musculature and ligaments
- relative heaviness of the head
  - all contributes to high degree of hypermobility that predisposes child's cord to ischemic necrosis

### How does one manage the child w/ SCI?

- retention
  - place Foley, leave for as short time as possible
  - start CIC ASAP
- UDS at 4-6 weeks, repeat at 2/12, 8/12, and 2 yrs
- periodic imaging
  - r/o stone formation, BOO

### What is the typical bladder function like in the child as they age?

- infants
  - typically void regularly, usually hourly
  - voids stimulated by feeding
  - 2/3 occur during sleep
  - not complete nor coordinated > 50% of the time
    - take 2-3 small voids to completely empty the bladder
    - typically 30% PVR
    - discoordinated pattern w/ bladder instability
  - very high pressures: up to 100cm H<sub>2</sub>O is normal
- child
  - as child matures, gradually achieve adult pattern of control

### What events must occur for the child to achieve an adult voiding pattern?

- bladder capacity must increase
  - by age 2, voiding q2h
- voluntary control over periurethral striated muscle
  - usually occurs by age 3
- direct volitional control over spinal reflex that controls the detrusor smooth muscle → most complex

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- ability to voluntarily initiate or inhibit detrusor contraction
- occurs usually by age 4

### How can one classify the dysfunctional elimination syndromes (DES)?

- Mild
  - Giggle incontinence
  - Postvoid dribbling
  - Daytime urinary frequency syndrome
  - Nocturnal enuresis
- Moderate
  - Unstable bladder: most common pattern of urinary dysfunction in childhood
    - urgency incontinence syndrome
    - small-capacity hypertonic bladder
    - continent bladder instability
  - Infrequent voiding syndrome
  - Functional bowel disturbances
    - constipation or fecal retention
- Severe
  - non-neurogenic neurogenic bladder (Hinman's syndrome or occult neuropathic bladder)

### What is the normal bladder wall thickness for a child on US?

- 3mm full, 5mm empty

### What are the clinical features of the non-neurogenic neurogenic bladder?

- Hx
  - present after toilet training and before puberty
  - nocturnal and diurnal UI
  - dribbling, overflow, and urge incontinence
  - bowel dysfunction: encopresis, constipation, and fecal impaction
  - recurrent UTI
  - stressful family environment
- Px
  - palpably enlarged bladder
  - DRE: normal sphincter tone, fecal impaction

### What are the findings during imaging of the non-neurogenic neurogenic bladder?

- US
  - bladder appears neuropathic
  - pear or dumbbell shape
  - thick wall w/ diverticulae or large capacity smooth walled bladder
  - upper tract dilation
- VCUG
  - large PVR
  - may appear like PUV w/ dilated prostatic urethra
  - VUR in 50%

### What is the cause of Hinman's syndrome?

- voiding against a closed sphincter to create a functional obstruction
  - voluntary dyssynergia b/w detrusor and striated muscle sphincter during voiding
  - pattern of voiding that is transitional b/w infant and adult types

### What is the Ochoa syndrome?

- inherited pattern of voiding dysfunction (AR)
  - identified in Colombian children
  - features of both neuropathy and Hinman's
- UI, constipation, VUR, hydro, bladder instability
- peculiar painful-appearing facial expression during laughter (like 6<sup>th</sup> CN palsy)

### What is the treatment for the non-neurogenic neurogenic bladder?

- follow treatment of neurogenic bladder

## Chapter 64 Questions - Voiding dysfn.doc

- urine sterilized
- bladder retraining
  - psychological support
  - suggestion therapy
  - biofeedback
- bowel function needs to be normalized
  - adjust diet
  - use laxatives
- medical therapy
  - anticholinergics
  - sympatholytics
  - Valium
- psychologic counselling
- parental education
- CIC if more severe upper tract dilation

### What is the etiology of the unstable bladder in children?

- functional or organic delay in CNS maturation
  - does not represent a neuropathy

### What are the features of the unstable bladder in children?

- Clinical
  - urgency, frequency: 60-70%
  - urge incontinence
    - not present in 1/3 of kids w/ instability → at expense of increased Pves
  - UTI: not common
  - Vincent's curtsy: almost pathognomonic for unstable bladder
    - child squats w/ heel of 1 foot compressing perineum and urethra to prevent leakage
  - described as never having been toilet trained
- Urodynamic
  - bladder hyperactivity during bladder filling
  - child attempts to constrict EUS to stay dry
    - if child does not void: high Pves occurs
    - if child voids: voiding is normal w/ low Pves, as EUS is relaxed
  - small-capacity hypertonic bladder
    - subcategory, characterized by more severe sx
    - DSD causing functional obstruction
- US
  - bladder wall thickening
- VCUG
  - smooth walled bladder w/ normal capacity
  - VUR in small capacity hypertonic variant

### What is the management of the unstable bladder in children?

- UDS
  - not required in all cases: reserved for children that fail empiric trial of anticholinergics
- MR spine
  - in older child that suddenly develops UI → r/o tethered cord
- anticholinergics
  - mainstay of treatment
  - decrease hyperactivity, increase the threshold volume at which contractions occur
- bladder retraining + diet/laxative program
  - fluid restriction
  - eliminate caffeine
  - frequent voiding

### What are the features of the infrequent voiding syndrome (busy little girl syndrome)?

- Hx
  - more common in girls
  - dry at night

## **Chapter 64 Questions - Voiding dysfn.doc**

- do not void upon wakening
- may not void for 8-12 hrs unless reminded
- US
  - bladder not thickened
  - no hydro
- usually no DSD

### **What is the treatment of the infrequent voiding syndrome?**

- bladder retraining
  - timed voiding
  - voiding diary
  - prevent constipation

### **How does fecal retention affect the bladder?**

- alters shape of BN and urethra
- causes bladder instability

### **What is giggle incontinence?**

- inherited condition
- detrusor hyperreflexia during laughter
- try simple measures first
- anticholinergics usually not helpful

### **What is the usual cause of postvoid dribbling?**

- usually in normal girls after toilet training
- due to vaginal reflux
  - improves w/ age
  - have child face back of toilet

### **Describe the epidemiology of nocturnal enuresis.**

- Rules of 15
  - 15% of 5-year olds wet
  - 5% of 10-year olds wet
  - 1% of 15-year olds wet
  - 15% of enuretics have encopresis
  - 15% of enuretics become dry each year
  - 15% of enuretics have daytime sx
  - 15% of enuretics have an initial dry period
  - 15% of nonenuretics have nocturnal polyuria
  - 15% of nonenuretics have nocturnal awakenings
- > 80% of enuretics wet only at night
- more F than M are dry
- NE 50% more common in M
- most have never been dry → primary enuresis

### **What are the features of NE?**

- Clinical
  - appear to be very deep sleepers, but in fact sleep no more deeply than normal children
  - "hard to awaken" reported by parents
- Urodynamic
  - reduced bladder capacity
  - low incidence of bladder instability
  - children do not void w/ bladder contraction

### **What are the different types of enuretic episodes seen by UDS in children w/ NE?**

- gradually undulating increases in Pves, culminating in wetting
- very quick void associated w/ minimal body movement
- complete parasomnia: total lack of CNS reaction and response to bladder filling

### **What are the types of enuretic episodes seen by EEG?**

## Chapter 64 Questions - Voiding dysfn.doc

- Type I: stable bladder w/ EEG response
- Type II: stable bladder w/o EEG response
- Type III: unstable bladder w/o EEG response

### What is the etiology of NE?

- Developmental delay
  - major cause in most children
- Urodynamic
  - normal contractions
- Sleep
  - normal sleep
- Vasopressin secretion and urine production
  - many kids w/ NE have similar levels of VP during day and night
    - leads to larger amounts of dilute urine produced at night
    - VP levels may be low due to bladder being empty from NE
  - circadian VP levels mature over time
- Heredity
  - NE is inherited: 77% chance if both parents wet during childhood, 43% if one parent, 15% if neither
  - AD with variable penetrance: ENUR1 gene on chromosome 13
  - M > F
- Organic GU tract disease
  - obstructive lesions: meatal stenosis and stricture → cause daytime sx as well, never just NE
- Misc
  - psychologic disturbances
  - ADHD

### What is the treatment for NE?

- discourage tx before age 7: no successes prior to this age
- Medical therapy
  - anticholinergics: disappointing
  - imipramine: cures enuresis in 40-50%, improves in another 10-20%
    - 25mg if age 5-8, 50mg if older
    - s/e: personality changes, sleep/appetite changes, GI sx, nervousness
  - DDAVP
    - should not be used as 1<sup>st</sup> line
    - 20-40µg for nasal spray, 200-400µg for pill
    - produces state of antidiuresis, significantly reduces wet nights
    - lasts 7-12h
    - temporary effect: 50-90% relapse if stopped
    - s/e: hyponatremia + seizures
      - ◆ must limit fluids
- Behavioural modification: first line approach for NE
  - bladder retraining
    - increase interval b/w voids
    - responsibility reinforcement: stars, charts, etc.
  - wet alarm: most effective means of eliminating bedwetting
  - have child change sheets: will become annoyed and stop wetting
  - parental understanding and commitment

### What are the worrisome signs and sx in children w/ voiding dysfunction?

- Signs
  - lumbosacral spine abnormalities: hair, lipomas, cutaneous dimples/tracts, bony irregularities
  - reduced anal sphincter tone
  - fixed low urinary specific gravity
  - palpable bladder
- Sx
  - day and night sx
  - dysuria
  - rectal pain
  - penile pain or d/c



#### **Chapter 64 Questions - Voiding dysfn.doc**

- vaginal pain or d/c
- straining to void



**Chapter 65**  
**• Hypospadias •**

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**What is a hypospadias?**

- association of 3 anatomic and developmental anomalies of the penis:
  - abnormal ventral opening of penile meatus
  - abnormal ventral curvature (chordee)
  - abnormal distribution of foreskin: dorsal hood, deficiency ventrally

**How can one classify hypospadias?**

- Anterior (distal) – 50-70%
  - glanular
  - coronal
  - subcoronal
- Middle
  - distal penile
  - midshaft
  - proximal penile
- Posterior (proximal)
  - penoscrotal
  - scrotal
  - perineal

**Describe the embryologic formation of the urethra.**

- development begins at 4<sup>th</sup> week
- urethral groove established by the development of the urethral folds on the ventrum of the urogenital sinus
- urethral folds fuse ventrally in midline by 11<sup>th</sup> week

**What different theories explain the embryologic formation of the distal urethra?**

- ectodermal ingrowth theory
  - distal glanular urethra formed by lamellar ingrowth of the surface epithelium (ectodermal origin)
  - becomes stratified squamous at completion
- endodermal differentiation theory
  - urethral plate extends to tip of phallus
  - maintains patency and continuity throughout urethral development
  - epithelium of entire urethra originates from UGS (endoderm)

**Describe the neurovascular anatomy of the hypospadiac penis.**

- nerves that innervate the penis originate proximally as 2 well-defined bundles under the pubic rami superior and lateral to urethra
  - same for normal and hypospadiac penis
- as 2 crural bodies converge into corpora cavernosa, nervous tissue fans out from 11 and 1 o'clock positions
  - does not remain confined to 2 well-defined bundles
- extensive vascularity of the distal urethral spongiosum and glans in hypospadiac compared w/ normal penis

**What is the etiology of hypospadias?**

- multifactorial
  - environmental or other endocrine disruptor
    - exposure to progesterone
    - IVF: progesterone given early in pregnancy
  - local tissue abnormality or native endocrine abnormality
    - abnormal androgen production by fetal testis
      - ◆ insufficient T or DHT production

## Chapter 65 Questions - Hypospadias.doc

- ◆ severe deficiency of 3 $\beta$ -hydroxysteroid dehydrogenase enzyme
- limited androgen sensitivity in developing external genitalia: defects in AR quality or quantity
- ◆ Reifenstein's syndrome (partial androgen resistance)
- arrested development
- premature cessation of androgenic stimulation due to premature involution of Leydig cells of fetal testis
- delay in maturation of hypothalamic-pituitary-testis axis

### What are the potential causes of chordee in hypospadias?

- abnormal development of the urethral plate
- abnormal fibrotic mesenchymal tissue at the urethral meatus
- corporal disproportion or differential growth of normal dorsal corpora and abnormal ventral tissue

### How can one classify chordee without hypospadias?

- Devine and Horton (1973)
  - Type I: most severe
    - very thin "mucous membrane" urethra and deficiency of corpus spongiosum from site of curvature to glans penis
    - presence of dense fibrous tissue beneath urethra is cause of curvature
  - Type II
    - urethra surrounded by normal corpus spongiosum w/ abnormal Buck's and dartos fascia
  - Type III
    - only dartos fascia is abnormal
- Donnahoo (1998)
  - skin tethering
  - fibrotic dartos and Buck's
  - corporal disproportion

### What is the incidence of hypospadias?

- Sweet: 1 in 122
  - 87% coronal or glandular
- children of pts w/ hypospadias: 6-8%
- brothers of pts w/ hypospadias: 14%
- twins: 8.5X risk

### What anomalies are associated w/ hypospadias?

- Genetics
  - abnormal karyotype: only in posterior hypospadias
  - syndromes: 49 recognized
- GU
  - cryptorchidism: 8-9%
  - hernia/hydrocele: 9-16%
    - increased in more proximal hypospadias
  - intersex state
    - more likely to have intersex if gonads nonpalpable
    - 2/3 rule: suspect intersex if bilateral UDT or hypospadias + unilateral UDT

### What are the indications for surgical intervention of hypospadias?

- correction of deformities that interfere w/ function of urination and procreation

### What is involved in the evaluation of the child w/ hypospadias?

- Intersex evaluation
  - for those w/ posterior hypospadias
- Radiologic
  - no routine imaging if isolated hypospadias, esp if middle or anterior in location
  - more important in pts w/ posterior hypospadias: VCUG
- Hormonal manipulation
  - controversial
    - hCG vs. T ointment
  - increases penile size and length, allows for more simple repairs
  - prepubertal exogenous T does not adversely affect penile growth

## Chapter 65 Questions - Hypospadias.doc

### What are the general principles of hypospadias repair?

- Orthoplasty
  - assess penile curvature: photo taken at home, artificial erection after shaft degloving (NS, pharmacologic)
- Urethroplasty
  - neourethral formation
    - immediately adjacent tissue
    - local flaps (fasciocutaneous flaps – dartos): based on branches of deep and superficial external pudendal vessels
    - local or extragenital free grafts
  - neourethral coverage (2<sup>nd</sup> layer)
    - subcutaneous (dartos) flap: must incise glans wings deeply to accommodate extra tissue
    - tunica vaginalis
      - ◆ testis delivered into field, vaginalis incised, and flap isolated from testis and mobilized on pedicle
    - corpus spongiosum: uses paraurethral tissue as 2<sup>nd</sup> layer
- Meatoplasty + Glanuloplasty
- Skin coverage
  - ventral transfer of preputial skin w/ buttonhole or Byars flaps (midline split w/ lateral transfer)

### What are the techniques used to manage penile curvature?

- skin release and transfer
- plication and Heineke-Miculicz techniques
  - removal of transversely oriented segments of tunica albuginea from the longer convex aspect of the penis
  - lengthening of shorter convex surface by Heineke-Miculicz principle
- tunica albuginea plication
  - parallel lines of incision 1cm in length and 5-10mm apart are marked bilaterally after degloving penis and dissecting NVB
  - outer edges of the parallel incisions approximated w/ 4-0, shortening long corporal surface
- corporal rotation
  - medial rotation and suture fixation
    - maintains maximal penile length
- grafts
  - dermal grafts
    - ideal for the short phallus w/ severe curvature
    - dermal graft harvested from non-hair bearing site (groin), defatted, placed in NS
    - transverse incision made at point of maximal curvature, graft sutured w/ 6-0
  - tunica vaginalis graft
- total penile disassembly
  - can correct glans tilt, ventral curvature w/o hypospadias, and curvature w/ hypospadias

### When does one perform hypospadias repair?

- before 1 yr of age
  - higher complication rate in older pts

### What is involved in the pre- and post-op care of hypospadias pts?

- Pre-op
  - GA
  - local anaesthetic: 0.25% Marcaine as penile block will decrease penile pain
  - antibiotics: one IV dose pre-op
- Post-op
  - dressing: no advantage

### How can one prevent post-op erections after hypospadias repair?

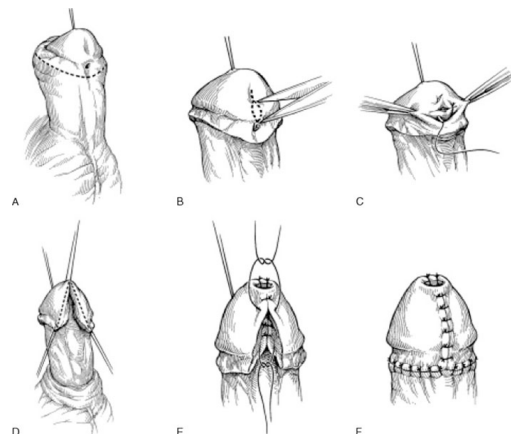
- ketoconazole: reduces adrenal and testicular androgen production through inhibition of 17,20-desmolase
  - prevents conversion of cholesterol to T
- amyl nitrate

### Describe the intraoperative algorithm used for hypospadias repair.

- Assess native anatomy
  - meatal location
  - penile curvature

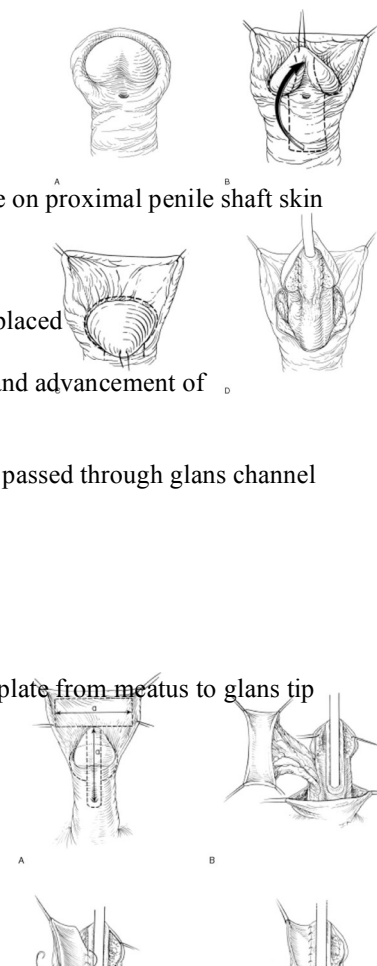
## Chapter 65 Questions - Hypospadias.doc

- penile size
- ventral and proximal skin
- Deglove penile shaft skin
- Preserve urethral plate
- Assess penile curvature
  - no curvature
    - one-stage urethroplasty
    - 2<sup>nd</sup> layer coverage
    - meatoplasty, glanuloplasty, skin coverage
  - mild-moderate curve
    - dorsal orthoplasty
    - one-stage urethroplasty
    - 2<sup>nd</sup> layer coverage
    - meatoplasty, glanuloplasty, skin coverage
  - severe curvature
    - orthoplasty: dorsal or ventral +/- distal division of urethral plate
    - urethroplasty: 1 or 2 stage technique
    - 2<sup>nd</sup> layer coverage of neourethra
    - meatoplasty, glanuloplasty, skin coverage



## How can one classify the various techniques used for hypospadias repair?

- Anterior hypospadias procedures
  - Advancement techniques
    - MAGPI
      - ◆ circumferential incision 5-7mm proximal to corona
      - ◆ incise distal glanular groove, approximate transversely in Heineke-Miculicz fashion → advances meatus
      - ◆ ventral edge of meatus pulled distally w/ stay suture
      - ◆ medial edges trimmed and approximated in 2 layers
    - Arap MAGPI modification
      - ◆ incorporation of urethroplasty (distal tubularization) w/ meatal advancement and glanuloplasty
    - distal urethral circumferential dissection and advancement
    - BEAM (bulbar elongation anastomotic meatoplasty)
  - Tubularization techniques
    - Thiersch-Duplay urethroplasty: simple urethral plate tubularization
    - GAP (glans approximation procedure)
    - TIP (tubularized incised plate) urethroplasty: 2-5% complications
  - Flap techniques
    - Mathieu
      - ◆ measure length of defect from meatus to glans tip and measure equal distance on proximal penile shaft skin
        - ◆ usually 7.5mm width for proximal flap, tapered to 5.5mm distally
      - ◆ glans wings incised deeply, penile shaft skin degloved
      - ◆ penis assessed for curvature → orthoplasty
      - ◆ tissue folded over at the meatus, bilateral longitudinal running subQ sutures placed
    - Barcat balanitic groove technique
      - ◆ similar to Mathieu, but includes dissection of urethral plate distal to meatus and advancement of approximated (tubularized) flaps to tip of the glans
    - Mustarde
      - ◆ combination of a perimeatal-based ventral skin flap which is tubularized and passed through glans channel to get meatus at penile tip
  - MIP
    - "pyramid" procedure: specific for MIP
- Middle hypospadias procedures
  - Onlay techniques
    - Onlay island flap (OIF)
      - ◆ urethral plate measured to 6mm, parallel longitudinal incisions outlining the plate from meatus to glans tip
      - ◆ preputial skin marked, incised, and dissected w/ pedicle
      - ◆ rectangular preputial flap held w/ fine stay in each corner
      - ◆ ensure reaches anast w/o tension
      - ◆ tubularize over 6F Silastic catheter
    - split prepuce in situ onlay



## Chapter 65 Questions - Hypospadias.doc

- ◆ ½ of split prepuce used for island flap is isolated by de-epithelializing adjacent inner prepuce
- ◆ outer skin of preputial onlay is de-epithelialized
- ◆ onlay flap sutured to urethral plate /w 7-0
- double onlay preputial flap
- Tubularization techniques
  - King
  - TIP urethroplasty
- Posterior hypospadias
  - One-stage repairs
    - Onlay techniques
      - ◆ Onlay island flaps
      - ◆ Onlay-tube-onlay urethroplasty
        - ◆ central tubularized segment w/ distal and proximal onlay components
      - ◆ double-onlay preputial flap: preputial onlay segment is harvested transversely and transposed ventrally w/ buttonhole in vascular pedicle
    - Tubularization techniques
      - ◆ Transverse preputial island flap (TPIF) aka. "Duckett tube"
        - ◆ traction sutures, urethral meatus marked circumferentially
        - ◆ skin incised, penis degloved
        - ◆ penis assessed for curvature: may require division of the urethral plate
        - ◆ transversely oriented rectangle of preputial skin marked
          - length = distance from urethral meatus to glans tip
          - width = 15mm
        - ◆ skin incised, tubularized over 6F Silastic, transferred tension-free to ventral penis
          - sutured line of anastomosis is facing dorsally
        - ◆ core of glans tissue excised, distal tube passed through glans channel
        - ◆ proximal then distal anastomoses performed: running, locking, full-thickness
      - Other
        - ◆ modified TPIF: incorporation of proximal non-hirsute interscrotal tissue
        - ◆ parametatal foreskin flap (aka "manta wing flap" or "clergyman's stole")
        - ◆ radical bulbar dissection
    - Two-stage repair
      - 1<sup>st</sup> stage
        - ◆ orthoplasty: use interposition dermal graft inlay after transverse incision of cavernosa at maximal curvature
          - ◆ glans deeply incised in ventral midline distally to point of neomeatus
        - ◆ repositioning of prepuce ventrally: prepares well-vascularized tissue to be used for urethroplasty
      - 2<sup>nd</sup> stage: 6mo later
        - ◆ urethroplasty: tubularization in Thiersch-Duplay fashion
        - ◆ 2<sup>nd</sup> layer coverage w/ local subcutaneous tissues or tunica vaginalis flap
    - Free-graft
      - skin, bladder, buccal mucosa

### Describe the procedure of TIP urethroplasty.

- stay sutures placed
- urethral plate and circumferential incisions marked
- parallel longitudinal and longitudinal incisions made
- **longitudinal incision in the urethral plate**
  - from penile meatus to level of hypospadiac meatus
  - depth depends on configuration of glanular groove
- urethral plate tubularized over 6F silastic catheter
  - do not close distal extent too tightly: **must fashion a wide meatus**
- **subcutaneous dartos tissue flap harvested from lateral or dorsal penile shaft and repositioned over urethra as 2<sup>nd</sup> layer**
  - tunica vaginalis flap may be used for a more proximal TIP repair
- glans penis reapproximated in 2 layers
- catheter secured

### What are the indications for 2-stage repair of hypospadias?

- scrotal or perineal hypospadias
- severe curvature

## Chapter 65 Questions - Hypospadias.doc

- small penis

### What are the complications of hypospadias repair?

- Early post-op
  - bleeding/hematoma: most common complication → may require drainage if large
  - infection: uncommon due to excellent blood supply → get cultures, start antibiotics, debride if necessary
  - ischemia of flaps
    - minimize post-op edema, hematoma
    - conservative management initially, silver sulfadiazine cream if small eschar or debride, graft if severe
  - repair breakdown: conservative mgmt if small, steri-strips if larger → must r/o infx, hematoma
- Late post-op
  - urethrocutaneous fistula
    - dx: retrograde injection of dye (methylene blue)
    - tx depends on size, location, and time from OR:
      - ◆ small fistulae may occasionally close
      - ◆ larger/multiple fistulae may require incision of intact skin bridges and delayed repeat repair in 6-12mo
    - r/o chordee, stricture, diverticulae: calibrate urethra distal to fistula w/ bougie
  - meatal stenosis
    - usually due to technical issues: too narrow a lumen, too tight glanuloplasty
    - tx: dilation, meatotomy, flap reconstruction if severe
  - urethral diverticulae
    - may be associated w/ distal stricture or meatal stenosis
    - tx: excision and multilayered closure
  - BXO: may occur after hypospadias repair
    - tx: steroids, bladder or buccal mucosal free grafts → do not use skin grafts, as may recur (up to 50%)
  - recurrent penile curvature
    - may be due to fibrosis of reconstructed urethra, corporeal disproportion
    - may require elevation of the neourethra, division of restrictive tissues in the intercorporeal septum, division of the neourethra, dorsal plication
  - urethral stricture
    - most commonly at proximal anastomotic site of TPIF
    - characterize stricture w/ cysto
    - tx: dilation → VIU → patch, pedicled flap urethroplasty
      - ◆ do not do multiple VIU or dilation: will worsen fibrosis
  - hair in urethral lumen: if hair-bearing skin used for reconstruction
  - hypospadias cripples, psychiatric consequences

### What are the causes of urethrocutaneous fistula in hypospadias repair?

- distal stricture/stenosis
- failure to invert epithelial edges
- devitalization of tissue
- no 2<sup>nd</sup> layer of urethroplasty coverage

### What are the causes of repair breakdown after hypospadias repair?

- tension
- excessive electrocautery
- unidentified vascular pedicle injury
- hematoma

### When can one safely attempt reoperative hypospadias repair?

- after 6mo from 1<sup>st</sup> OR
- after all edema, infection, and inflammation have resolved
- healing is complete

### What are the potential techniques one can use for reoperative hypospadias repair?

- local tissue flap
  - immediately adjacent or local pedicled well-vascularized tissue: preferred
    - reoperative TIP procedure: results similar to primary repair, no preputial skin needed
  - OIF: rarely usable
  - tunica vaginalis flap: not used due to high rate of meatal stenosis and urethral stricture (60%)

### **Chapter 65 Questions - Hypospadias.doc**

- free grafts
  - bladder mucosa
  - buccal mucosa
  - 2 stage: STSG as 1<sup>st</sup> stage, then tubularization at 2<sup>nd</sup> stage for hypospadias cripple

### **What are the advantages of the OIF vs. TPIF?**

- OIF has decreased fistula rate compared w/ TPIF







## **Chapter 66**

### **• Abnormalities of the Genitalia in Boys and their Surgical Management •**

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#### **What is the normal penile length for the newborn?**

- 3.5 +/- 0.7cm length  
→ should be at least 1.9cm long
- 1.1 +/- 0.2cm width

#### **How often does the penile midline raphe deviate, and what is its significance?**

- 10%, usually to L
- may be associated w/ torsion or chordee w/o hypospadias

#### **What is the natural hx of physiologic phimosis?**

- as penis grows, smegma accumulates under the prepuce
- gradually separates foreskin from glans
- intermittent erections cause foreskin to become completely retractable
- by 3 yrs: 90% of foreskins can be retracted  
→ < 1% have phimosis by 17yrs

#### **What is the treatment of physiologic phimosis?**

- tx only in boys > 4-5 yrs or those that develop balanitis  
→ topical corticosteroid cream (0.1% dexamethasone, or triamcinolone [Kenalog] ) daily x 4-6 weeks QID
- do not forcefully retract foreskin: recurrent adhesions from inflammation

#### **What are the indications for circumcision in boys w/ phimosis?**

- boys > 7-8 yrs w/ phimosis resistant to steroid
- phimosis that causes ballooning
- recurrent balanitis

#### **How does one counsel a parent regarding neonatal circumcision?**

- Hx/Px
- Reasons to circumcise
  - carcinoma of the penis: only in men that were not circumcised at birth
  - increased risk for UTIs for boys in 1<sup>st</sup> year of life (20X)
  - ? decreased risk for STDs: controversial
    - may be more likely to get HIV, genital ulcers
  - prevention of phimosis and balanitis
- Reasons not to circumcise
  - must weigh risks vs. benefits
  - contraindications: hypospadias, chordee w/o hypospadias, dorsal hood deformity, webbed penis, or small penis

#### **What is the s/e of prilocaine in EMLA cream?**

- methemoglobinemia

#### **What are the complications of circumcision?**

- bleeding  
→ usually from frenulum
- wound infection
- penile adhesions
- remove too much skin  
→ apply antibiotic ointment, adherent gauze  
→ most of the skin grows back: skin graft will disfigure the penis
- secondary phimosis w/ trapped or buried penis
- injury to glans/urethra/penile shaft

## Chapter 66 Questions - Penis problems.doc

- partial glans removal: suture back to penis
- penile necrosis from thermal injury
- ablative penile injury: ?gender reassignment w/ bilateral orchiectomy → unresolved
- meatal stenosis
  - due to inflammation after circumcision or cutting of frenular artery
- inadvertent injection of epinephrine: tx w/ infiltration of 0.4mg phentolamine

### What are the sx of meatal stenosis?

- forceful fine stream
- dorsally deflected stream
- prolonged voiding time
- LUTS, UI

### What is the normal size of the urethral meatus in boys?

- 6 weeks – 3 yrs: 10F
- 4-10 yrs: 12F
- 11-12 yrs: 14F

### What is the management of meatal stenosis?

- urethral calibration
- RBUS + VCUG if hx UTI
- meatoplasty: in office w/ EMLA if possible
- corticosteroid if BXO

### What are the most common cystic lesions of the penis?

- accumulation of smegma under the unretractable foreskin

### What are the forms of inconspicuous penis?

- webbed penis
  - scrotal skin extends onto the ventrum of the penis
  - corrected by incising the web transversely, separating penis from scrotum, and closing it transversely (Heineke-Miculicz)
    - may also perform circumcision w/ Byars' flaps transferred to ventral surface of penis, excising redundant tissue
- concealed (buried or hidden) penis
  - normally developed penis that is camouflaged by the suprapubic fat pad
  - indications for surgery: controversial
    - only in adolescents, as younger boys often lose fat pad
  - prepuce unfurled and used for skin coverage, subcutaneous tissue on dorsal penis fixed to pubic fascia
- trapped penis
  - phallus embedded in suprapubic fat pad after circ
  - may predispose child to UTIs and retention
- micropenis
  - normally formed penis that is at least 2.5SD below the mean in size
  - usually ratio of length:width is normal
  - testes usually undescended

### What are the causes of micropenis?

- Deficient T secretion
  - Hypogonadotropic hypogonadism: most common
    - isolated, including Kallman's
    - associated w/ other pituitary hormone deficiencies (ex: CHARGE association)
    - Prader-Willi
    - Laurence-Moon-Bardet-Biedl
    - Rud's syndrome
  - Primary hypogonadism
    - anorchia
    - XXY
    - gonadal dysgenesis (incomplete)
    - LH R defects (incomplete)
    - Noonan's

## Chapter 66 Questions - Penis problems.doc

- Down's
- Robinow's
- LMBB syndrome
- Defects in T action
  - GH/IGF-1 deficiency
  - AR defects (incomplete)
  - 5 $\alpha$ -reductase deficiency (incomplete)
  - fetal hydantoin syndrome
- Developmental anomalies
  - aphallia
  - cloacal exstrophy
- Idiopathic
- Associated w/ other congenital malformations

### What is the management of micropenis?

- karyotype
- pediatric endocrinology consult
- T levels before and after hCG stimulation
- GnRH stimulation test
- glucose, lytes, cortisol, TSH
- MRI head: assess pituitary
- androgen therapy: for penile growth stimulation
  - T enanthate IM 25mg qmonthly x 3 mo
  - may ultimately reduce growth response at puberty

### What is penile torsion?

- rotational defect of the penile shaft
  - usually rotated in counterclockwise direction
  - penile size normal
- correction unnecessary if < 60°
  - if severe, may have to mobilize base of penis to identify and incise dysgenetic bands of tissue

### What is the cause of lateral or dorsal curvature of the penis?

- overgrowth or hypoplasia of one corporeal body
  - usually congenital
- tx: Nesbit procedure

### What is genital lymphedema?

- impaired lymphatic drainage that causes progressive penile or scrotal swelling
  - Milroy's disease: congenital lymphedema
  - Meige's disease: occurs later in childhood

### What is the treatment of genital lymphedema?

- observation initially
- surgical therapy if significant or progresses
  - remove all involved tissue
  - penis degloved and all tissue b/w Buck's and skin is excised, as well as redundant penile skin
  - penis may be covered w/ local flaps or STSG

### What is megaprepuce?

- severely redundant inner foreskin covering normal glans penis
- ++ penoscrotal swelling during voiding
  - discomfort or UTI
- tx: deglove penis, excise redundant skin

### What is the cause of aphallia?

- failure of development of the genital tubercle
- rare: 1 in 10,000,000

### What malformations are associated w/ aphallia?

## **Chapter 66 Questions - Penis problems.doc**

- cryptorchidism
- VUR
- horseshoe kidney
- renal agenesis
- imperforate anus
- MSK and CVS anomalies

### **What is the management of aphallia?**

- karyotype
- evaluation: full team of GU, endocrine, psych
- ?gender reassignment

### **What is the typical configuration of congenital urethral fistula?**

- urethra and meatus are normal
- fistula is usually coronal or subcoronal
- may be associated w/ imperforate anus or ventral chordee

### **What are the other names for penoscrotal transposition?**

- scrotal engulfment
- bifid scrotum
- doughnut scrotum
- prepenile scrotum
- shawl scrotum

### **What anomalies are associated w/ penoscrotal transposition?**

- perineal, scrotal, or penoscrotal hypospadias w/ chordee
- caudal regression
- Aarskog syndrome
- sex chromosome abnormalities
- GU tract abnormalities
  - in up to 75%

### **What is the tx of penoscrotal transposition?**

- hypospadias repair
  - TPIF w/ Thiersch-Duplay tubularization of the proximal urethra
- scrotoplasty
  - circumscribe the superior aspect of each ½ of the vertical aspect of the scrotum and extend these incisions laterally
  - traction sutures placed on superior aspects of scrotal flaps
  - scrotal wings rotated medially and sutured together under penis in midline
  - Penrose x 24-48h

### **What is the most common location for ectopic scrotum?**

- along inguinal canal
  - usually suprainguinal

### **What anomalies are associated w/ ectopic scrotum?**

- cryptorchidism
- inguinal hernia
- exstrophy
- popliteal pterygium syndrome
- upper GU tract anomalies
  - renal agenesis
  - renal dysplasia
  - ectopic ureter
- perineal lipoma

### **What is bifid scrotum?**

- labioscrotal folds completely separated
  - usually associated w/ proximal hypospadias

## **Chapter 66 Questions - Penis problems.doc**

### **What is scrotal hypoplasia?**

- underdevelopment of one or both sides of the scrotum
  - usually associated w/ UDT

### **How can one classify vascular lesions of the genitalia?**

- hemangiomas
  - on the skin, present at birth
  - may grow postnatally then slowly involute
  - congenital hemangiomas
    - strawberry: most common type
      - ◆ result from proliferation of immature capillary vessels
      - ◆ usually require no treatment
      - ◆ can use short-term PO steroids, surgical excision
    - subcutaneous hemangiomas (aka cavernous hemangiomas): less common
      - ◆ tend to enlarge gradually
      - ◆ "bag of worms" sensation
      - ◆ tx: excision en bloc w/ preoperative angioembolization
- vascular malformations
  - in subcutaneous tissues, present at birth
  - tend to persist and enlarge





## **Chapter 67**

### **• Abnormalities of the Testes and Scrotum and their Surgical Management •**

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#### **Describe the embryology of testes formation.**

- male sexual differentiation does not occur until 7th week
  - testicular differentiation initiated by SRY gene
- 4-6 weeks: genital ridges organize
  - primordial germ cells located along caudal wall of the embryonic yolk sac near allantoic stalk migrate to genital ridges via the dorsal mesentery
  - gonadal primordium arises from thickening of coelomic epithelium b/w root of mesentery and mesonephros
  - coelomic epithelium develops epithelial cords (germinal cords) into underlying mesenchyme to form genital ridges
- Sertoli cells develop by 7th week
- Leydig cells develop by 8th week
  - fetal testis begins to secrete T and MIS independent of pituitary hormone secretion
  - T secreted by Leydig cells converted to DHT
  - DHT induces differentiation of Wolffian duct into the epididymis and vas
  - MIS secreted by Sertoli cells, causes degeneration of the Mullerian structures after 8th week
- gubernaculum appears by 7th week
  - extends from the gonad to the fascia b/w the developing external and internal obliques
  - composed of undifferentiate spindle-like cells w/ a large amount of extracellular material containing GAGs
  - ridge persists b/w gonad and diaphragm: cranial suspensory ligament (CSL)
    - regresses as gubernaculum proliferates during testicular descent
- external genitalia develop b/w 8th and 10th week
- germ cells differentiate into gonocytes to become fetal spermatogonia by 15 weeks
- testes lie dormant w/i abdomen until 23rd week
  - inguinal transit occurs in matter of days
  - by 30 weeks, most are descended into the scrotum

#### **What is the incidence of an undescended testes (UDT)?**

- 3% at birth
  - 70-77% descend, usually by 3 months
  - 1% at 1 year
- unilateral more common than bilateral
- 30% in premature infants

#### **What are the RF for UDT?**

- preterm
- small-for-gestational age
- LBW
  - birth weight is the principal determinant of UDT at birth and at 1 yr
- twins
- congenital malformations
- pre-eclampsia
- breech presentation
- delivery by C-section
- FHx UDT
- ?Asian background

#### **What factors predict complete spontaneous descent of UDT by 3 months?**

- LBW
- bilateral UDT
- normal scrotal anatomy
  - poorly rugated or small scrotum, hypospadias → more likely to be cryptorchid at 3mo



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- testes that are positioned lower along the normal path of descent

### How can one classify UDT?

- palpable vs. nonpalpable
- location
  - intra-abdominal
    - usually just inside the internal ring
    - "peeping" testis: if lies inside ring itself
  - intracanalicular: within the inguinal canal
    - usually difficult to palpate
  - extracanalicular
    - suprapubic: lies just beyond the external ring
    - infrapubic: lies just below the pubis, just outside the scrotum
  - ectopic
    - completes normal transinguinal migration, but is misdirected outside the normal path of descent below external ring
    - most common location = Denis-Browne pouch (superficial pouch b/w external oblique and Scarpa's)
    - other locations: transverse scrotal, femoral, perineal, and prepenile ectopia
  - ascended testis

### What is the definition of a retractile testis?

- withdrawn out of the scrotum by an active cremasteric reflex
- can easily be brought down into an orthotopic position within the scrotum → remains there after traction released
- usually found within the groin
- monitor regularly until puberty, until testes no longer retractile

### What is meant by testicular ascent?

- any testis documented to be scrotal and later found to be undescended
- 4 types:
  - infantile (true): testis documented in scrotum during 1<sup>st</sup> year, later found to be UDT
    - true UDT w/ patent hernia
  - childhood (true): older children that present w/ true UDT (age 3-12)
    - nearly all have patent processus vaginalis, shortened cord structures
  - ectopic: most common form
    - ectopic attachments allow testis to hang into scrotum
    - w/ linear growth, testis ascends to ectopic position
  - post-surgical: after inguinal hernia repair
    - cord or testis caught up in scar tissue
    - w/ linear growth, testis becomes undescended
    - will not descend spontaneously or w/ hormones

### What are the phases of testicular descent?

- nephric displacement by degeneration of the mesonephros: 7-8 weeks
- transabdominal → passage from metanephros to internal ring: completed by 21-23 weeks
  - results from differential growth of lumbar vertebral column and pelvis
- transinguinal transit → at 28 weeks
- extracanalicular migration from external ring to scrotum → completed by 30 weeks

### What factors may affect testicular maldescent?

- Endocrine
  - Androgens
    - androgens do not mediate the transabdominal phase of testicular descent
      - ◆ required for inguinal-scrotal phase of descent
    - can be caused by decreased LH synthesis, impaired LH or GnRH R, impaired AR (AIS), or T synthesis
      - ◆ errors in T synthesis: CYP17 deficiency,  $\beta$ -HSD type 2 deficiency, 17 $\beta$ -HSD type 3 deficiency, 5 $\alpha$ -R type 2 def
  - MIS
    - MIS secreted by Sertoli cells, responsible for regression of Mullerian ducts
    - levels normally surge in 1<sup>st</sup> year, peak at 4-12 mo, then decrease w/ age
    - pts w/ cryptorchidism have no surge, levels are decreased

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- likely has no role in regulation of testicular descent
- Estrogens
  - prenatal tx w/ DES: associated w/ urogenic abnormalities
    - ◆ impair gubernacular development
    - ◆ cause persistence of Mullerian duct structures
- Descendin
  - androgen independent factor → gubernacular specific growth factor
  - believed to be secreted from the testis in androgen-independent fashion
- Gubernaculum
  - possible functions:
    - guide into the scrotum: no firm attachment → does not pull testis into the scrotum
    - wedge that swells and dilates the inguinal path
  - is the major factor responsible for testicular descent
- GF nerve and CGRP
  - transection of GF in rats causes UDT
  - androgens increase the # of GFN cell bodies and promote gubernacular migration
  - CGRP is a NT in the GF nerve
- Epididymis
  - unknown if epididymal abnormalities are the cause or result of UDT
  - epididymis precedes testis into the scrotum
  - abnormality in epididymis in 40-90% of UDT
- Intra-abdominal pressure
  - conditions w/ decreased IAP: prune-belly, cloacal exstrophy, omphalocele, gastroschisis
  - more significant role in transinguinal descent

### What histopathologic hallmarks are associated w/ UDT?

- decreased # of Leydig cells: earliest postnatal abnormality in UDT
- degeneration of Sertoli cells
- delayed disappearance of gonocytes
- delayed appearance of adult dark (Ad) spermatogonia
- failure of primary spermatogonia to develop
- reduced total germ cell counts
  - may see all above in contralateral testis as well, but to lesser extent

### What are the consequences of UDT?

- infertility
  - orchidopexy may not reduce this risk
  - post-pubertal orchidopexy: 83% azoospermic or oligospermic
  - paternity compromised in men w/ bilateral (but not unilateral) UDT, not correlated w/ age at orchidopexy
- testicular cancer
  - men w/ UDT at increased risk of testicular cancer
  - RR 40X greater: controversial if orchidopexy reduces this risk
  - higher the position of UDT, greater the risk
  - seminoma most common
- hernia
  - patent processus vaginalis in > 90% of UDT
  - higher incidence of epididymal abnormalities in boys w/ patent processus
- testicular torsion

What RF are recognized for infertility in previously cryptorchid men?

- increased FSH
- low sperm count
- parenchymal testicular suture at time of orchidopexy

### What are the potential causes for increased risk of testis ca in UDT?

- exposure of testis to increased temp
- intrinsic pathologic process affecting both testes

When a child is referred for UDT, what is the chance the testis is absent?

- testis palpable in 80%

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- testis not palpable in 20%
  - 20% absent
  - 30% atrophic
  - 50% intra-abdominal

### What is involved in the workup of a child w/ UDT?

- Hx
  - preterm and maternal hx: use of gestational steroids
  - perinatal hx: scrotal exam at birth
  - child's medical and surgical hx
  - FHx cryptorchidism or syndromes
- Px
  - child must be relaxed, supine
  - examine w/ warm hands and soapy water
  - penile malformations: hypospadias, micropenis, ambiguous genitalia
  - scrotum: asymmetry, underdevelopment
  - inguinal canal: ?testis
  - hernia/hydrocele
  - contralateral testicular hypertrophy
- Radiology
  - overall accuracy of radiologic testing for UDT: 44% → not useful
- Ix
  - hCG stimulation test
    - can be administered to induce T production
    - may be false -ve if Leydig cells unresponsive to exogenous hCG
  - FSH: if FSH increased, further work-up not needed → likely represents bilateral anorchia
    - if LH/FSH increased, do hCG stim test

### What are the principles of treatment for UDT?

- identify anatomy, position, and viability of testes
- identify any potential coexisting syndromes
- place testis in scrotum w/ permanent fixation
- prevent further testicular damage
- treat by 1 year of age

### What are the options for treatment of UDT?

- Hormonal therapy
  - exogenous hCG 1500 IU/m<sup>2</sup> IM q3d x 4 weeks: stimulates Leydig cells to produce T directly
  - exogenous GnRH or LHRH: stimulates pituitary to release LH
    - nasal spray 1.2mg/day for 4 weeks
  - successful treatments more common in testes that are lower down, unilateral UDT
  - reascent in up to 25%, overall efficacy in < 20% for cryptorchid testes
- Surgery
  - orchidopexy
  - orchiectomy: usually reserved for post-pubescent males w/ contralateral normal testis

### What are the s/e of hCG treatment for UDT?

- increased rugation and pigmentation of the scrotum
- increase in penis size
- increase in weight velocity

### What are the options for surgical treatment of UDT?

- Open
  - 1-stage Fowler-Stephens
  - 2-stage Fowler-Stephens
  - abdominal orchidopexy
  - inguinal orchidopexy
  - high scrotal orchidopexy
  - low scrotal orchidopexy
  - testicular autotransplantation

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- Laparoscopic
  - 1-stage Fowler-Stephens
  - 2-stage Fowler-Stephens
  - abdominal orchidopexy

### Describe the technique of orchidopexy for UDT.

- EUA prior to placement of caudal/epidural: occasionally a nonpalpable testis will become palpable
- transverse inguinal skin incision
- dissect down to external oblique
- open external oblique fascia
  - preserve ilioinguinal ligament
- dissect out distal gubernacular attachments
  - must visualize vas (if long looping) to prevent injury
- dissect away cremasteric muscular fibers
- tunica vaginalis opened
- complete mobilization of the testis and spermatic cord
  - complete transection of fibers b/w cremasteric and internal oblique
  - separate patent processus from spermatic cord
  - dissect internal spermatic fascia from cord
  - separate vas from vascular elements
  - retroperitoneal dissection if necessary
- transverse midscrotal superficial skin incision made within rugal skin fold
  - develop dartos pouch
- fixation suture 5-0 or 6-0 Prolene into tunica of testis
- snap passed over pubis from inguinal incision into scrotum passing suture
- orchidopexy performed
  - must have no tension
- scrotal incision closed w/ fine interrupted absorbable suture
- external oblique closed to recreate external ring
- close skin

### Describe the laparoscopic approach to orchidopexy.

- port placement
  - 5mm umbilical port
  - 2 x 3mm ports, inferior to umbilicus in MCL
  - if unilateral, can lower contralateral port
- dissection of cord
  - 2mm trocars placed
  - peritoneum incised lateral to vessels
- distal peritoneal incision
  - anterior to processus, caudal to vas
  - maintain the triangle b/w the two
  - allows plane behind cord, gubernaculum
- divide gubernaculum
  - can occasionally be left intact
  - watch for long looping vas
  - use cautery
- form neocanal
  - 2mm grasper passed anterograde
  - medial or lateral to inferior epigastrics if needed
  - generally lateral to medial umbilical ligament
- deliver testis
  - neocanal is radially dilated
  - grasper passed through scrotal trocar
  - gentle traction to avoid avulsion
- gain extra length if needed
  - incise peritoneum over vessels as needed

### What is the success rate for orchidopexy?

- 1-stage Fowler-Stephens: 67%

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- 2-stage Fowler-Stephens: 77%
- abdominal orchidopexy: 81%
- inguinal orchidopexy: 89%
- upper scrotal orchidopexy: 92%

### What are the indications for transparenchymal suture fixation?

- tethered testis when its position is tenuous after complete mobilization, requiring fixation to nylon button
- testicular fixation of ipsilateral and contralateral testis due to clinical torsion

### What ancillary techniques can be used to gain additional cord length during orchidopexy?

- complete mobilization of cremasterics
- mobilization of spermatic vessels medially
- Prentiss maneuver: incision of floor of inguinal canal, dividing inferior epigastrics → positions spermatic vessels medially
- retroperitoneal dissection
- ligation of patent processus vaginalis above external ring
  - prevents adherence of peritoneum to spermatic vessels
- staged orchidopexy: 2<sup>nd</sup> stage 6-12 mo later

### How does one manage the intra-abdominal testis?

- laparoscopy
  - possible to place clip on vessels as 1<sup>st</sup> stage of F-S
  - Prentiss maneuver to divert exit of testis medial to inferior epigastrics
- Fowler-Stephens orchidopexy
  - gonadal vessels limit distal mobility: ligation of testicular vessels to improve
  - blood supply dependent on artery to the vas and the cremasteric artery
  - 1 stage: must preserve wide pedicle of peritoneum w/ vas to maintain collateral blood flow
    - best candidates: long looping vas that extends down into the inguinal canal
  - F-S test: clamp gonadal artery temporarily, look at testis for color changes
    - do 2 stage if tenuous blood supply
- microsurgical autotransplantation
  - suture to inferior epigastric artery
  - success 80%
  - indication: solitary, high intra-abdominal testis
  - can give T or hCG preop to improve vascular caliber
  - use Gibson incision

### What are the potential findings at laparoscopy for nonpalpable testis?

- blind-ending vessels above internal ring
  - no further investigations necessary → "vanishing" testis
- vascular cord structures entering internal ring
  - even if hypoplastic vessels seen entering ring, inguinal exploration mandatory
  - if internal ring is open, possible intra-inguinal testis → remove if nubbin
- intra-abdominal testis

### What are the complications of orchidopexy?

- testicular retraction
- hematoma formation
- ilioinguinal nerve injury
- torsion post-op
- damage to vas
- testicular atrophy
  - due to skeletonization of cord, torsion of vessels during passage to scrotum, ligation during F-S, ++ tension

### What is the cause of hydrocele?

- accumulation of fluid within tunica vaginalis +/- patent processus vaginalis

### How can one classify hydrocele?

- simple hydrocele
  - obliterated communication

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- deserve long-term observation → most resolve by 2 years
- **aspiration is contraindicated: may get infected, spread into peritoneum**
- communicating hydrocele
  - persistence of processus vaginalis
  - Sx
    - size changes during day → smaller in morning
    - worse as day progresses, w/ activity, increases in IAP, fever
    - transilluminates
  - must explore through inguinal incision, isolate sac from cord, and ligate at internal ring
- hydrocele of the cord
  - presents as painless groin mass, may change in size
  - tx: high ligation of patent processus
- abdominoscrotal hydrocele: large bilobed hydrocele spans entire inguinal ring → remove entire abdominal component

### What are the indications for contralateral exploration in pts w/ inguinal hernia?

- past or present hx of contralateral inguinal or scrotal pathology
  - incidence of patent processus vaginalis 50-60%
- hx of VP shunt or other source of increased intraperitoneal fluid (ex: PD)

### What is the DDX of the acute/subacute scrotum?

- Torsion
  - torsion of cord
  - torsion of appendix testis/epididymis
- Infection
  - epididymitis
  - orchitis
- Hernia
- Hydrocele
  - simple
  - communicating
  - hydrocele of the cord
- Trauma/insect bite
- Cancer
- Varicocele
- Spermatocele
- Dermatologic lesion
- Vasculitis
  - HSP
- Idiopathic
- Nongenital pathology: adductor tendinitis

### What is the cause of intravaginal torsion?

- lack of normal fixation of an appropriate portion of the testis and epididymis to fascial and muscular coverings
  - "bell clapper" deformity
  - creates an abnormally mobile testis that hangs freely within the tunical space

### How long does it take for irreversible ischemic injury to occur after torsion?

- 4 hours
  - degree of torsion may have an influence over potential for viability

### What is the presentation of testicular torsion?

- Hx
  - acute onset of scrotal pain
    - may be more gradual in some cases
  - hx of prior episodes of severe, self-limited scrotal pain and swelling
    - may be intermittent torsion
  - N/V
  - can occur in relation to exercise, but is usually spontaneous
    - pts often wakened from sleeping
  - usually no LUTS

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- Px
  - high-riding testis
  - abnormally transverse orientation
  - absence of a cremasteric reflex

### What is the tx of testicular torsion?

- can attempt manual detorsion in ER
  - may not completely correct the rotation, and exploration still required
- imaging: only use radiologic studies to confirm lack of torsion
  - Doppler US: determine blood flow
    - sensitivity 89%, specificity 99%
  - Radionuclide imaging
- surgical exploration
  - median raphe scrotal incision
  - examine testis, detorse, place in warm sponges
  - examine after several minutes
  - remove necrotic testes
  - after exploration, dartos pouch w/o fixation
  - must explore contralateral side → almost always find bell-clapper deformity in contralateral side

### What is the presentation of torsion of the testicular and epididymal appendages?

- extremely variable
  - insidious onset to acute onset, identical to testicular torsion
- localized tenderness to upper pole
- may see infarcted appendage through skin: "blue dot" sign
- scrotal wall edema, erythema
- cremasteric reflex should be present
- testis should be mobile

### What is the treatment of torsion of an appendage?

- nonoperative management usually
- acute exploration if need to r/o testicular torsion
- excision of torsed appendage if failure to resolve inflammation and pain

### What is the presentation of epididymitis in boys?

- Sx
  - pain
  - swelling and tenderness of epididymis
  - hx of UTI, urethritis, urethral discharge, sexual activity, urethral catheterization, GU surgery
  - hx HSP
  - hx amiodarone
- Px
  - cremasteric reflex should be present
- Ix
  - pyuria, bacteriuria, or +ve urine C&S

### What is the management of boys w/ epididymitis?

- Doppler or nuclear imaging to r/o torsion
- screen all boys w/ +ve urine C&S w/ RBUS and VCUG
- limitation of activity
  - bed rest for 1-3 days may limit course
- scrotal elevation
- application of cold or warmth
- IV antibiotics if UTI suspected
- avoid urethral instrumentation
- prophylactic antibiotics until VCUG completed
- PO NSAIDs may resolve inflammation

### What is the GU involvement of HSP?

- systemic vasculitis that can cause scrotal swelling due to involvement of the testis, epididymitis, or both

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- scrotal involvement in 35%: swelling, erythema, and tenderness
- U/A: hematuria and proteinuria

### What is the typical presentation of perinatal torsion of the cord?

- hard, nontender testis fixed to overlying scrotal skin found at birth  
→ due to extravaginal torsion

### What is the management of perinatal torsion of the cord?

- no need for surgical exploration: zero salvage rates
- no need for contralateral exploration: not associated w/ bell-clapper deformity

### What is the typical presentation of pediatric varicocele?

- 90% L sided
- found in 15% of male adolescents
- most are asymptomatic: discovered on routine PHE

### By what mechanisms does varicocele adversely affect spermatogenesis?

- reflux of adrenal metabolites
- hyperthermia  
→ interference w/ countercurrent heat exchange
- hypoxia
- local testicular hormonal imbalance  
→ Leydig cell dysfunction due to decreased intratesticular T levels  
→ FSH/LH/T in serum not abnormal
- intratesticular hyperperfusion injury

### What histologic findings may be found in men w/ varicocele?

- decreased spermatogenesis
- maturation arrest
- tubular thickening
- Leydig cell abnormalities: atrophy, hyperplasia  
→ more pronounced on ipsilateral side

### What are the indications for treatment of varicocele in adolescents?

- symptomatic
- decreased testis volume  
→ testis size should be within 20% or 2cc

### What d/o are associated w/ agenesis of the vas?

- CF: CBAVD seen in 65-95% of men w/ CF  
→ related to CFTR gene
- absence of other portions of the Wolffian duct derivatives  
→ 75% have only head of epididymis, 20% have no ipsi epididymis  
→ 86% have ipsi SV agenesis, 20% have bilateral SV agenesis
- must screen all men w/ vas agenesis w/ renal US → r/o URA

### What is the *persisting mesonephric duct*?

- junction of the vas and ureter  
→ failure of incorporation of the distal mesonephric duct (common excretory duct) to become incorporated into the UGS  
→ ipsilateral kidney usually poorly functioning → renal dysplasia
- may present w/ UTI or epididymitis
- associated w/ imperforate anus

### How can one classify epididymal attachment anomalies?

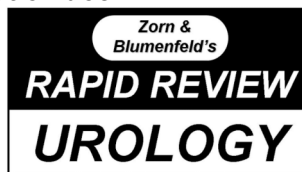
- fusion anomalies  
→ cause caput epididymis to be detached from the testis
- suspension anomalies  
→ other segments of the epididymis are poorly attached to body of testis



**Chapter 67 Questions - UDT + hernias.doc**

**What d/o are associated w/ epididymal cysts (spermatocele)?**

- VHL
- offspring of women tx w/ DES



## **Chapter 68**

### **• Sexual Differentiation: Normal and Abnormal •**

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#### **What is the gene responsible for determining gonadal differentiation?**

- SRY (sex-determining region y gene)
  - elaborates TDF (testis-determining factor)
  - on short arm of Y chromosome near centromere, adjacent to pseudoautosomal boundary

#### **What genes other than SRY have been implicated in sex differentiation?**

- WT-1
  - oncogene on chromosome 11 involved in development of Wilms'
  - exerts its effects upstream of SRY, necessary for commitment and maintenance of gonadal tissue
  - influences formation of the bipotential gonad affecting testicular and ovarian development
- SF-1
  - regulates MIS
  - expressed in all steroidogenic tissue: adrenal cortex, testis (Leydig cells), ovarian theca, granulosa cells, corpus luteum
- SOX-9
  - similar to SRY, expressed in testes
  - likely involved in gonadal differentiation
- DSS (DAX-1)

#### **How does a duplicated X chromosome cause XY sex reversal?**

- expresses double dose of gene normally subject to X inactivation
  - DSS: dosage-sensitive sex reversal
  - DAX-1: implicated in adrenal gland hypoplasia → may inhibit testis determination

#### **When is estrogen synthesis detectable in the female embryo?**

- just after 8 wks

#### **How can one classify abnormal sexual differentiation?**

- Disorders of gonadal differentiation
  - Klinefelter's (47XXY)
  - Seminiferous tubule dysgenesis
  - 46XX male
  - Syndromes of gonadal dysgenesis
    - Turner's (45XO)
    - Pure gonadal dysgenesis
    - Mixed gonadal dysgenesis (MGD)
    - Dysgenetic male pseudohermaphroditism
    - Bilateral vanishing testes/testicular regression syndromes
  - True hermaphroditism (TH)
- Female pseudohermaphroditism
  - CAH: 21-hydroxylase, 11 $\beta$ -hydroxylase, 3 $\beta$ -HSD deficiencies
  - maternal androgens
- Male pseudohermaphroditism
  - Leydig cell agenesis/unresponsiveness
  - Variants of CAH affecting corticosteroid and T synthesis
    - congenital lipoid adrenal hyperplasia
    - 3 $\beta$ -HSD, 17 $\alpha$ -hydroxylase deficiency
  - Disorders of T biosynthesis
    - 17,20-lyase deficiency
    - 17 $\beta$ -hydroxysteroid oxidoreductase deficiency
  - Disorders of androgen-dependent target tissue

## Chapter 68 Questions - Sexual differentiation.doc

- androgen R and post-receptor defects
- AIS: complete or partial
- androgen resistance in infertile men
- Disorders of T metabolism by peripheral tissues
  - 5 $\alpha$ -reductase deficiency
- Disorders of synthesis, secretion, or response to MIS
  - persistent mullerian duct syndrome
- Unclassified forms
  - micropenis
  - Mayer-Rokitansky-Kuster-Hauser syndrome

### What are the characteristics of Klinefelter's?

- eunuchoidism
  - decreased androgen production prevents normal secondary sexual characteristics
  - fat distribution is more female
- gynecomastia → 8X risk for breast cancer
- azoospermia
- increased gonadotropin levels
- small firm testes

### Why is Klinefelter's associated w/ abnormal secondary sexual development?

- seminiferous tubules degenerate and are replaced w/ hyaline
- serum T low-normal and gonadotropins are elevated
  - decreased androgen production prevents normal sexual development

### What are the characteristics of 46XX males?

- normal male external genitalia
  - hypospadias in 10%
- infertility in 100%
- either SRY +ve or -ve

### What mechanisms have been proposed to explain XX sex reversal?

- translocation of Y chromosome material: including SRY to X chromosome
- mutation of an autosomal or X chromosomal gene, permitting testicular differentiation downstream from SRY
- undetected mosaicism w/ Y-bearing cell line

### What is the treatment for 46XX males?

- similar to Klinefelter's
  - androgen replacement
  - reduction mammoplasty
  - surveillance for breast cancer

### What are the 4 classic features for Turner's?

- female phenotype
- short stature
- lack of secondary sexual characteristics
- somatic abnormalities
  - broad chest
  - widespread nipples
  - webbed neck
  - hypoplastic nails
  - pigmented nevi
  - aortic coarctation
  - renal anomalies: **horseshoe**, duplication/agenesis, malrotation, multiple renal arteries
  - streak ovaries
    - causes elevation in LH and FSH w/ decrease in estrogen and androgen

### What is the incidence of Turner's?

- 1 in 2500 live births

## **Chapter 68 Questions - Sexual differentiation.doc**

### **What karyotypes are possible for Turner's syndrome?**

- 45XO: 50%
- isochromosome X: duplication of 1 arm of X chromosome w/ loss of the other arm
- 45XO/46XX mosaic: 10-15%
- 45XO/46XY mosaic: 2-5%

### **What is the importance of 45X/46XY karyotype?**

- predisposes pts to potential masculinization and gonadoblastoma  
→ 30% chance of gonadoblastoma, as early as age 6 → remove both streak gonads

### **Why do the ovaries become streaks in Turner's?**

- follicular cells that normally surround the germ cells and provide a protective mantle are inadequate
- rate of attrition of oocytes is so rapid that by birth no oocytes remain → become streaks

### **What is the treatment of Turner's?**

- human GH: used to increase adult height
- exogenous hormone: induce puberty at 12-15 yrs
- cardiac surveillance
- ART for fertility

### **What are the characteristics of 46XX pure gonadal dysgenesis?**

- normal female external genitalia
- normal Mullerian ducts w/ absence of Wolffian duct structures
- normal height
- bilateral streak gonads
- sexual infantilism
- normal 46XX karyotype

### **What is the management of 46XX pure gonadal dysgenesis?**

- hormone replacement
- no need for GH: height normal

### **What is the difference in management of 46XX vs. 46XY pure gonadal dysgenesis?**

- 46XY pts are at risk of gonadoblastoma in streak gonads  
→ require gonadectomy

### **What are the characteristics of MGD?**

- unilateral testis (often intra-abdominal) w/ ipsi Wolffian duct, contralateral streak gonad and Mullerian duct  
→ testis has functioning Sertoli and Leydig cells, but no germinal elements → all are infertile
- persistent Mullerian structures  
→ uterus, vagina, and fallopian tubes present in almost all patients
- varying degrees of inadequate masculinization → 2<sup>nd</sup> most common cause of ambiguous genitalia (2<sup>nd</sup> only to CAH)  
→ phenotype varies from Turners → ambiguous → normal male  
➢ most pts have normal male genitalia  
→ varying degrees of phallic enlargement, UGS, labioscrotal fusion, and UDT  
→ most infants have normal appearing male external genitalia
- 45XO/46XY mosaic  
→ increased risk of gonadoblastoma, Wilms'

### **What malignancies have an increased incidence in pts w/ MGD?**

- germ cell tumours in streak gonad: gonadoblastoma
- Wilms' tumour  
→ part of triad in Denys-Drash (MGD, Wilms', renal mesangial sclerosis)

### **What is the management of MGD?**

- gender assignment
- appropriate gonadectomy
- screening for Wilms' tumour

### **What is dysgenetic male pseudohermaphroditism?**

## **Chapter 68 Questions - Sexual differentiation.doc**

- condition related to MGD
- 2 dysgenetic testes rather than 1 testis and 1 streak
- typically have 45X/46XY or 46XY karyotype

### **What are the characteristics of dysgenetic male pseudohermaphroditism?**

- spectrum of external genital abnormalities
- persistent Mullerian structures, dependent on MIS secretion by testes
- increased risk of gonadal malignancy: gonadoblastoma

### **What are the characteristics of 46XY complete gonadal dysgenesis?**

- normal female genitalia
- well-developed mullerian structures
- bilateral streak gonads
- nonmosaic karyotype
- major problem is sexual infantilism
  - present in teens w/ delayed puberty
  - amenorrhea, absent breast development
- high concentration of LH → increased androgen levels → clitoromegaly
- increased risk for germ cell tumours: gonadoblastoma

### **What is the treatment for 46XY complete gonadal dysgenesis?**

- bilateral gonadectomy
- hormone replacement

### **What is the difference b/w "embryonic testicular regression" and "bilateral vanishing testes?"**

- embryonic testicular regression = loss of testicular tissue in 1<sup>st</sup> trimester → ambiguity of external genitalia
- bilateral vanishing testes = male sexual differentiation took place, but loss of testes occur later

### **What are the potential causes for vanishing testes?**

- genetic mutation, teratogen, bilateral torsion

### **How can one make the diagnosis of bilateral vanishing testes?**

- 46XY karyotype, castrate T levels, elevated LH/FSH
- spectrum of phenotypes: complete female → ambiguity → normal male

### **What is the treatment for bilateral vanishing testes?**

- dictated by position in clinical spectrum
  - gender assignment
  - androgen or estrogen supplementation
  - prostheses

### **What is the definition of true hermaphroditism?**

- individuals who have both testicular tissue w/ well-developed seminiferous tubules and ovarian tissue w/ primordial follicles
  - 1 ovary and 1 testis, or 1-2 ovotestes

### **What are the characteristics of true hermaphroditism?**

- external genitalia: male, or ambiguous but masculinized
  - hypospadias and chordee in 80% raised as male
- internal structures: almost all pts have UGS, uterus usually present
  - ovotestis has fallopian tube in 2/3, vas or vas + tube in 1/3
- 2/3 are 46XX
  - 46XY, 46XX/XY mosaic, 46XX/47XXY less commonly
- can be fertile if raised as female w/ appropriate ductal structures
- increased risk of gonadal tumours: 10%

### **What is the treatment for true hermaphroditism?**

- gender assignment: 75% raised as male
  - based on functional potential of external genitalia, internal ducts, and gonads
- appropriate gonadectomy

## **Chapter 68 Questions - Sexual differentiation.doc**

- postop stimulation w/ hCG to confirm all testicular tissue removed
- surveillance for gonadal tumours

### **What is the most common cause for female pseudohermaphroditism?**

- CAH
  - formation of hydrocortisone impaired, w/ compensatory increase in ACTH
  - increases formation of adrenal steroids proximal to enzymatic defect, w/ increase in T

### **What enzymes can be involved in CAH?**

- 21-hydroxylase: 95% → most common, located on chromosome 6
- 11 $\beta$ -hydroxylase
- 17-hydroxylase
- 17,20-lyase
- 3 $\beta$ -hydroxysteroid dehydrogenase (HSD) → least common

### **What is the incidence of CAH?**

- 1 in 5000-15000
  - highest incidence in Yup'ik Alaskan Eskimo population: 1 in 490

### **How can one classify pts w/ CAH?**

- salt wasters: pt w/ virilization and aldosterone deficiency
  - 75% of CAH from 21-OH deficiency present w/ salt wasting, 25% w/ simple virilization
- simple virilizers: pts w/ virilization w/o salt wasting
- nonclassic pts: no virilization or salt wasting

### **What are the typical characteristics of the external genitalia in a female w/ CAH?**

- clitoromegaly
  - may appear to be hypospadiac penis
- labial fusion
- UGS

### **How do pts w/ salt-wasting CAH present?**

- sx begin after first few weeks of birth
  - failure to regain birth weight
  - weight loss
  - dehydration
  - adrenal crises in first 10-21 days
  - vomiting
  - death from hyperkalemia, dehydration, shock

### **How does the male without salt wasting present?**

- isosexual precocity within 2-3 years
  - enlarged penis, scrotum, prostate
  - pubic hair, acne, deepening of voice
  - well-developed musculature
  - bone age more advanced than appropriate for chronological age

### **How does the pt w/ non-classic 21-hydroxylase deficiency present?**

- hirsutism
- oligomenorrhea
- male pattern baldness
- PCOD
- oligospermia and subfertility in men

### **What is the cause of hypertension in non-classic 11 $\beta$ -hydroxylase deficiency?**

- increased serum levels of deoxycorticosterone (DOC)

### **What are the biochemical findings in pts w/ classic 21-hydroxylase deficiency CAH?**

- increased progesterone and 17-hydroxyprogesterone
- increased urinary 17-ketosteroids and pregnanetriol

## Chapter 68 Questions - Sexual differentiation.doc

### What are the characteristics of 3 $\beta$ -HSD deficiency CAH?

- various degrees of incomplete masculinization
  - small phallus, hypospadias w/ labioscrotal fusion, UGS, blind-ending vaginal pouch
- scrotal testes
- normal Wolffian ducts
- normal Sertoli cells: absent Mullerian structures
- salt-losing crisis soon after birth
- increased serum levels of 17-OHprogesterone and DHEA

### What is the treatment for CAH?

- control electrolytes and BP
- hydrocortisone as steroid replacement initially
- fludrocortisone 0.05-2.5mg OD as maintenance
- prenatal treatment w/ dexamethasone to prevent virilization
- feminizing genitoplasty at 3-6 months
  - ? prophylactic adrenalectomy: controversial

### How can one make the prenatal dx of CAH in the at-risk fetus?

- measurement of amniotic fluid for 17-OHprogesterone

### How does prenatal treatment of CAH prevent virilization?

- dexamethasone crosses placenta, suppressing fetal secretion of ACTH, preventing virilization
  - start at 5-6 weeks of gestation: cannot confirm dx before therapy is started
  - long-term effects unknown

### How can one check for effectiveness of therapy in pts w/ CAH?

- measure morning plasma 17-hydroxyprogesterone

### What maternal agents have been associated w/ female virilization?

- danazol: T derivative used to treat endometriosis
- progestins
- maternal ovarian or adrenal tumours: arrhenoblastoma, hilar cell tumour, lipoid cell tumour, ovarian stromal cell tumour, luteoma of pregnancy, Krukenberg's tumour

### What is meant by male pseudohermaphroditism?

- 46XY pts w/ differentiated testes who have varying degrees of feminization phenotypically
  - impaired male differentiation due to inadequate secretion of T, inability of target tissue to respond (AR defects), or impaired MIS production

### What are the characteristics of Leydig cell aplasia?

- 46XY karyotype: AR trait
- female phenotype w/ sexual infantilism
- testes palpable in inguinal canals or labia majora
- no Mullerian structures
- short vagina
- low T, elevated LH

### What biochemical test is characteristic of Leydig cell aplasia?

- absence of T rise after hCG stimulation test

### What is the rate limiting step in acute steroid synthesis?

- steroidogenic acute regulatory protein (StAR)
  - stimulates cholesterol transport from the outer to the inner mitochondrial membrane
  - conversion of cholesterol to pregnenolone

### What are the characteristics of pts w/ StAR deficiency?

- 46XY
- female or ambiguous external genitalia
- blind-ending vaginal pouch

## **Chapter 68 Questions - Sexual differentiation.doc**

- intra-abdominal or labial testes
- absence of Mullerian structures (functioning Sertoli cells, normal MIS levels)
- rudimentary Wolffian structures
- present in 1<sup>st</sup> few weeks of life w/ adrenal insufficiency and salt wasting
  - hyponatremia, hyperkalemia, metabolic acidosis
- large lipid laden adrenal glands on CT

### **What is the biochemical abnormality in pts w/ 17 $\alpha$ -hydroxylase deficiency?**

- impaired cortisol production, causing ACTH hypersecretion
- increased levels of DOC, corticosterone, and 18-hydroxycorticosterone
  - mineralocorticoid activity: salt and water retention, hypertension, hypokalemia

### **What are the characteristics of 17 $\beta$ -OHsteroid oxidoreductase deficiency?**

- normal female phenotype at birth
- well-differentiated testes found intra-abdominally
- puberty: phallic growth and progressive development of male secondary sexual characteristics
  - increased muscle mass, pubic/axillary/facial hair
  - testes may become palpable
- late onset of virilization due to pubertal increase in FSH/LH production, which may partially overcome the block in T synthesis

### **What are the characteristics of complete AIS?**

- 46XY: X linked trait
  - mapped to Xq11-12
- bilateral testes
- normal female external genitalia: decreased axillary and pubic hair
- absence of Mullerian structures
- short blind ending vagina
- pts usually diagnosed from primary amenorrhea or finding of testis at hernia repair
- normal levels of T, DHT, and gonadotropins
  - at puberty, LH/FSH levels increase, leading to increased levels of plasma estradiol, which causes feminization (including breast development)

### **What is the incidence of AIS?**

- 1 in 20,000-60,000 males

### **Why is vaginostomy required before herniorrhaphy in female patients?**

- to confirm presence of cervix
  - 2% of apparently female pts w/ hernia have 46XY and AIS

### **What are the different forms of androgen receptor abnormality identified in AIS?**

- decreased amount of normal receptor
- absence of receptor binding
- qualitatively abnormal receptor
- other receptor-+ve forms

### **What is the management of AIS?**

- Dx
  - karyotype
  - pelvic US to confirm absence of mullerian tissue
  - vaginal exam to confirm blind-ending vagina
  - hCG stim test
- can leave testes in until puberty complete → testes produce testosterone which becomes esterified peripherally, promoting breast development, signaling the onset of puberty
  - exception: palpable testes, testes associated w/ hernia
  - confirm complete AIS rather than partial → may get virilization at puberty w/ painful clitoromegaly
- gonadectomy → early gonadectomy prevents these problems
  - parents can select time for puberty w/ hormone replacement
  - delayed gonadectomy felt to be safe



## **Chapter 68 Questions - Sexual differentiation.doc**

### **What is Reifenstein's syndrome?**

- partial AIS: X linked
  - mildest form: infertile male syndrome

### **What are the characteristics of partial AIS?**

- ambiguity of external genitalia
- classic: male w/ perineoscrotal hypospadias, cryptorchidism, rudimentary Wolffian duct structures, gynecomastia, infertility
- can range from hypospadias and pseudovagina to gynecomastia and azoospermia
- at puberty: gynecomastia

### **What are the 2 forms of receptor defect in partial AIS?**

- reduced # of normally functioning androgen receptors
- normal receptor #, decreased binding affinity

#### **How can one diagnose partial AIS?**

- Px: ambiguous male genitalia
- karyotype: 46XY
- US: absent Mullerian structures
- normal T, DHT

### **What is the treatment of partial AIS?**

- delayed gonadectomy
- surgical reconstruction

### **What are the 2 forms of 5 $\alpha$ -reductase, and where are they expressed?**

- Type 1: expressed in liver, skin, prostate, external genitalia
- Type 2: prostate and external genitalia

### **What are the characteristics of pts w/ 5 $\alpha$ -reductase deficiency?**

- penoscrotal hypospadias → ambiguous genitalia
- small phallus
- UGS w/ separate vaginal and urethral openings and labioscrotal fusion
- short blind-ending vaginal pouch
- testes located in labia, inguinal canals, or abdomen
- vasa terminate in blind-ending vaginal pouch
- partial masculinization at puberty

### **What are the endocrine anomalies in 5 $\alpha$ -reductase deficiency?**

- elevated mean plasma T
  - T alone enough to stimulate Wolffian duct development
- low DHT levels
  - critical for development of normal external genitalia in utero

### **What is persistent Mullerian duct syndrome?**

- a.k.a. hernia uteri inguinale
- pts w/ 46XY karyotype, normal male external genitalia, but internal Mullerian duct structures

### **What are the characteristics of PMDS?**

- phenotypic males
- unilateral or bilateral undescended testes
- bilateral Fallopian tubes
- uterus
- upper vagina draining into a prostatic utricle

### **How can one classify pts w/ PMDS?**

- location of gonads
  - bilateral intra-abdominal testes
  - 1 testis in hernia sac or scrotum + contralateral inguinal hernia
  - both testes in same hernia sac (transverse testicular ectopia)

## **Chapter 68 Questions - Sexual differentiation.doc**

### **What is the etiology of PMDS?**

- heterogeneous disorder
- decreased secretion of MIS or abnormality of MIS receptor

### **What is the treatment for PMDS?**

- orchidopexy
- preserve necessary Mullerian structures to avoid vasa  
→ no malignancy in retained Mullerian structures

### **What is Mayer-Rokitansky-Kuster-Hauser syndrome, and how does it present?**

- congenital absence of the uterus and vagina
- upper GU anomalies in 1/3: renal agenesis, pelvic kidney, horseshoe
- presents w/ primary amenorrhea

### **What is the treatment for MRKH?**

- surgical creation of a neovagina

### **Describe the evaluation and management of a newborn w/ ambiguous genitalia.**

- History
  - FHx of infant death, intersex
  - infertility, amenorrhea, hirsutism
  - maternal medications: steroids, BCP during pregnancy
- Physical
  - gonads: palpable = testis
  - hypospadias
  - penile size: stretched < 2cm is ambiguous
  - clitoral size: >7mm is ambiguous
  - labia/scrotum: fusion, rugation, color/hyperpigmentation
  - presence of uterus (on DRE)
- US
  - define Mullerian anatomy
  - presence of: uterus, gonads, adrenals
  - ovotestis: cyst within a gonad
- Karyotype
  - buccal smear: simple but unreliable
  - peripheral leukocytes better
- Labs
  - electrolytes
  - T, DHT
  - 17-hydroxyprogesterone on day 3-4 to r/o 21-OH deficiency
    - stress of delivery may result in physiologic elevation in 1<sup>st</sup> few days of life
  - DHEA, DOC
  - LH, FSH
  - hCG stim test
- Radiology
  - retrograde studies of UGS
- Laparoscopy if undescended testes → biopsy +/- gonadectomy
- Endoscopy
- Gender assignment
  - fertility
  - risk of malignancy
  - long-term follow-up

### **What are the points that must be addressed in the pt w/ abnormal sexual differentiation?**

- chromosomes: karyotype
- testicular determinant factors
- gonads
- paracrine system: hormones + MIS
- internal duct structures: Mullerian vs. Wolffian
- endocrine system

## **Chapter 68 Questions - Sexual differentiation.doc**

- UGS
- external genitalia: phallus
- secondary sexual characteristics
- psychosexual identity
- fertility
- sexual function

### **What are the Wolffian and Mullerian derivatives in the male and the female?**

- Wolffian
  - Male: epididymis, vas, ejaculatory duct, SV, appendix epididymis
  - Female: Gartner's duct, Gartner's cysts
- Mullerian
  - Male: appendix testis, prostatic utricle
  - Female: uterus, Hydatic of Morgagni

### **What is the "Jost" principle of ductal differentiation?**

- differentiation of the internal genitalia is dependent on the presence of T produced by Leydig cells and the presence or absence of MIS produced by Sertoli cells

### **What are the various different names for partial AIS?**

- Reifenstein's syndrome
- Gilbert-Dreyfus syndrome
- Lubs syndrome

### **What are the options available for clitoral reconstruction?**

- clitorectomy
  - loss of sensation
- clitoral recession
  - excise mid and distal segments of cavernosa, maintaining dorsal NVB to glans
  - can remove majority of erectile tissue, leaving a strip of tunica
- clitoral reduction
  - remove wedge from central portion of glans → nerve-free zone
  - glans secured to crura of corpora
  - clitoral shaft skin split in midline, secured to glans

### **What is the major determinant for the technique used for vaginoplasty?**

- position of vaginal confluence
  - low vaginal confluence: vaginal orifice distal to external urinary sphincter
    - perineal cutback procedure
    - flap vaginoplasty
  - high vaginal confluence: vaginal orifice proximal to EUS

### **What are the options for creation of a neovagina?**

- dilation of vaginal dimple: progressive dilation
- skin graft procedure: McIndoe procedure
- bilateral pudendal-thigh flaps
- sigmoid/ileum neovagina

### **Describe the levels of sex hormones throughout fetal development.**

- during 1<sup>st</sup> trimester, placental hCG stimulates LH receptor of fetal gonad
- after this, fetal GnRH completes genital maturation
- surge of LH and FSH at birth
  - diminishes after 6<sup>th</sup> month of life, remaining suppressed until puberty
- T and DHT parallel LH
  - fetal peak in 2<sup>nd</sup> trimester and shortly after birth

### **How can one diagnose presence or absence of testicular tissue?**

- hCG stimulation test
- presence of MIS in serum
- laparoscopy for testes

## **Chapter 68 Questions - Sexual differentiation.doc**

**Which syndromes place the pt at risk for malignancy later in life?**

- Turner's w/ XY mosaicism
- complete AIS
- true hermaphrodite w/ XY mosaicism
- MGD





## Chapter 69

### • **Surgery for Intersexuality, Cloacal Malformation, and Other Abnormalities of the Genitalia in Girls** •

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#### **Describe the embryologic formation of the vagina and uterus.**

- cloaca appears at beginning of 2<sup>nd</sup> week of gestation
- urorectal septum appears during 4<sup>th</sup> week
  - separates UGS ventrally from anal canal dorsally
  - consists of 2 components:
    - Tourneux's fold: develops along the coronal plane
    - Rathke's plicae: infoldings of the lateral walls
  - fuses w/ cloacal membrane
- fibromuscular node: results from the contact of the septum w/ cloacal membrane
- paired mullerian ducts form from coelomic epithelium
  - develop lateral to mesonephric ducts
  - cross medially to fuse in midline
- contact of uterovaginal primordium joins UGS and form mullerian tubercle
  - induces the formation of paired outgrowths called sinovaginal bulbs
  - cells within the sinovaginal bulbs form a cord of tissue that creates a distal vaginal plate
  - vaginal plate canalized in caudal to cranial direction to form distal vagina
- UGS distal to mullerian tubercle exstrophies and form vestibule
  - vaginal lumen separated from cavity of UGS by hymen

#### **How can one classify anomalies of the female genital system?**

- Obstructive
  - transverse vaginal septum
    - due to failure in fusion/canalization of UGS and mullerian ducts
    - usually <1 cm thick
    - upper 46%, middle 40%, low 14%
    - sx: amenorrhea and distended upper vagina
  - vaginal atresia
    - UGS fails to contribute to formation of the lower portion of the vagina
    - mullerian structures are not affected: uterus, cervix, and upper vagina are normal
    - transverse incision at hymenal ring, obstruction drained, and pull-through procedure performed
  - vaginal agenesis / MRKH / mullerian aplasia
    - congenital absence of the proximal portion of the vagina
  - cervical atresia
    - pt best served w/ TAH w/ vaginal replacement
  - female circumcision
  - duplication of the uterus and cervix w/ unilaterally imperforate vagina
    - Sx: abdo/pelvic mass that terminates in bluish bulge in lateral vaginal wall
      - ◆ do not present w/ amenorrhea
    - must r/o ipsilateral renal anomalies
- Non-obstructive
  - interlabial masses
    - labial adhesions: most common interlabial abnormality in pediatric urologic practice
    - introital cysts
      - ◆ paraurethral cysts (Skene's duct cysts)
        - ◆ represents dilation of the paraurethral glands: homologues of prostate
        - ◆ may displace urethral meatus, causing deflected urinary stream
        - ◆ often rupture spontaneously: can drain w/ small needle
      - ◆ Gartner's duct cysts

## Chapter 69 Questions - Intersex OR.doc

- ♦ cystic remnants of the wolffian duct system, found along anteriomedial wall of vagina
- ♦ covered ectopic ureter
- hymenal disorders
  - hymenal skin tags: normal, excise if bleeding
  - imperforate hymen
    - ♦ most common congenital obstructive anomaly of the female reproductive tract
- prolapsed urethra
- prolapsed ureterocele
- urethral polyp: represent either hamartomatous growth or response to inflammation
- vaginal rhabdomyosarcoma: grape-like cluster of tissue from posterior vestibule
  - excellent prognosis due to predominance of embryonal cell type and early detection due to bleeding

### What test is the gold standard for defining internal mullerian anatomy?

- MRI

### What is the incidence of vaginal agenesis?

- 1 in 5000

### What findings are associated w/ vaginal agenesis?

- Gyne
  - variable absence or hypoplasia of cervix, uterus, and tubes
    - normal but obstructed uterus or rudimentary in 10%
  - ovaries almost always present and functional
- GU
  - renal agenesis or ectopia: 74%
- MSk abnormalities in 10-20%
  - congenital fusion of the cervical vertebrae (Klippel-Feil syndrome)
  - scoliosis
  - abnormalities of the hands and face

### How can one classify MRKH?

- Type A (typical): symmetric uterine remnants and normal tubes
- Type B (atypical): asymmetric uterine buds or abnormally developed fallopian tubes
  - most associated findings in type B MRKH

### What is the MURCS association?

- MULLerian duct aplasia, Renal aplasia, and Cervicothoracic Somite dysplasia
  - generalized disordered development of mesodermal differentiation during 4<sup>th</sup> week of life

### What is the treatment of vaginal agenesis?

- Vaginal replacement
  - skin neovagina
    - nonoperative approach: dilators against perineal surface to create progressive invagination
      - ♦ can achieve functional vagina in 4-6mo
    - operative approach
      - ♦ McIndoe procedure: dissect canal b/w rectum and urethra and lining area w/ STSG
        - ♦ STSG taken from buttocks and tubularized over a stent
        - ♦ transverse incision at level of perineal dimple
        - ♦ potential space opened to level of peritoneal reflection
        - ♦ labia minora sutured around stent to prevent extrusion
      - ♦ high incidence of vaginal stenosis: must use dilators postop
        - ♦ Singapore flap - bilateral
  - intestinal neovagina
    - 3cm segment of sigmoid is isolated to create vagina
    - bowel anastomosed directly to perineal dimple
  - optimal timing of surgery controversial

### What are the indications for use of an ileal segment in the use of bowel vaginoplasty?

- rads to pelvis
- absence of large bowel (cloacal exstrophy)

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### What are the advantages and disadvantages of a bowel vagina over a skin vagina?

- Advantages
  - lubrication of mucus
  - reduced incidence of postop contracture
- Disadvantages
  - frequent need to wear pads due to chronic vaginal discharge
  - daily douching
  - increased transmission of bloodborne pathogens

### How can one classify female genital mutilation?

- Type I: complete or partial excision of the clitoris
- Type II: excision of the clitoris and a portion of the labia minora
- Type III: excision of entire clitoris and labia minora, incision along medial labia majora
  - anterior 2/3 of labia majora are approximated to cover urethra and introitus
- Type IV: excision of entire clitoris and labia minora w/ near-complete approximation of the labia majora
  - pinhole opening near posterior fourchette for urine and menses

### What is the etiology of labial adhesions?

- irritation
- infection
- local tissue trauma
- hypoenestrogenism
- sexual abuse: rare

### What is the treatment for labial adhesions?

- usually asymptomatic: treat only if symptoms
  - urine pooling in vagina can cause PVD and perineal irritation
- topical estrogens
  - if no separation after 2 weeks, manual separation
- surgical division

### What are the sx of imperforate hymen?

- bulge along the posterior aspect of the introitus
- palpable suprapubic mass
- if not dx until adolescence: amenorrhea, cyclic abdominal pain, bulging bluish hymen

### What groups are at increased risk of prolapsed urethra?

- prepubertal black girls
- postmenopausal white girls

### What are the proposed etiologies of prolapsed urethra?

- hypoenestrogenism
- abnormal connection b/w inner and outer circular muscle layers of distal urethra
- episodic increases in IAP

### What are the sx of prolapsed urethra?

- bleeding from edematous and friable mucosa
- spotting on underwear
- doughnut shaped mass w/ urethral meatus at center

### What is the tx of urethral prolapse?

- dx by passing catheter
- non-operative: recurrence rate of 67%
  - observation
  - topical steroids
- surgical tx
  - excision of redundant mucosa w/ suturing of normal urethra to vestibule

### What is the typical configuration of urogenital sinus anomalies?



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- persistent communication of the vagina w/ the urinary tract
  - almost always occurs within the urethra
  - entry into bladder has been seen

### How can one classify the groups of pts w/ urogenital sinus and cloacal anomalies?

- children w/ intersex states
  - UGS anomalies most often seen in this group, usually w/ CAH
- isolated pure urogenital sinus w/o external genital or rectal involvement
- persistent cloaca: associated rectal involvement, w/ all 3 systems entering a common channel

### What is involved in the evaluation of a child w/ a UGS anomaly?

- General
  - initial prompt evaluation to determine genetic gender, endocrinologic abnormalities, and gender of rearing
- Hx
  - medications
  - FHx of early infant death, electrolyte abnormalities, ambiguous genitalia
- Px
  - VS: htn w/ CAH
  - SP mass: distended bladder, hydrometrocolpos
    - may be severe in cloacal anomalies
    - usually due to preferential flow of urine into vagina w/ poor drainage
  - lower back: identify spinal cord anomalies, sacral dimple, hair patch, abnormal pigmentation, abnormal buttocks
  - genital exam: size of phallus, consistency of erectile bodies, curvature
  - location of anus
  - perineal orifice
    - single perineal orifice in persistent cloaca
    - genital transposition
    - blank-appearing perineum
  - ascites
    - develops from voiding into vagina w/ retrograde flow into uterus and out tubes
- karyotype
- Radiology
  - Xray
    - identify abdominal mass
  - US of abdomen/pelvis
    - kidneys, gonads, presence of uterus, pelvic anatomy
      - ◆ hydro very common in cloacal anomalies
    - document distended vagina or bladder
    - enlarged adrenal glands: CAH
  - genitography
    - cervical impression seen at the top of vagina documents presence of internal female organs
    - identify rectal and vaginal confluence
  - echo
    - to r/o other organ system anomalies
  - MRI lumbar spine: r/o lumbosacral spine anomalies
    - spinal cord anomalies in 43% of persistent cloaca
- Endoscopy
  - usually done at the time of reconstruction
  - done in 1<sup>st</sup> few days of life if needed to help w/ gender identity
- gonadal biopsy: rarely needed
  - open or laparoscopic
  - scrotal skin biopsy: in males w/ incomplete AIS

### What anomalies are associated w/ UGS anomalies?

- CVS: 13%
- CNS: 10%
- resp: 5%
- GI disorders
  - imperforate anus
  - TEF

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- duodenal atresia
- rectal duplication
- MSK
  - vertebral (esp sacral) anomalies: relatively common

### How can one classify UGS anomalies?

- based on vaginal location
  - Type I: labial fusion
  - Type II: distal confluence → majority
  - Type III: proximal or high confluence
  - Type IV: absent vagina

### What is the typical configuration of UGS and cloacal anomalies?

- urinary communication to cloaca urethral in 77%
  - virtually no urethra in 23%
- rectal entrance usually just at level of vaginal confluence
  - may be broad, or long narrow fistulous tract
  - may enter into vagina or bladder w/o communication to the cloaca
  - most common entrance is within septum of duplicated vagina, w/ all 3 joining cloaca together
  - rectal communication is vaginal in 68%, cloacal in 11%, rest in other locations

### What is involved in the surgical reconstruction of UGS?

- Initial management
  - stabilization of metabolic disorders
    - replace cortisol and fludrocortisone if CAH
  - determine sex of rearing
  - determine timing for reconstruction
    - clitoral surgery should be done in the neonatal period
    - optimal timing for vaginoplasty is controversial
      - ◆ vaginoplasty combined w/ clitoroplasty allows for redundant skin to be used
      - ◆ maternal estrogen stimulation allows for thicker vaginal tissue

### What are the steps of reconstruction of the masculinized female genitalia?

- clitoral reconstruction
  - must retain normal clitoral innervation for optimal sexual gratification
- vaginoplasty
  - posteriorly based perineal flap
- labial reconstruction

### What are the different types of vaginoplasty that can be used?

- cut-back vaginoplasty: used only for simple labial fusion
- flap vaginoplasty: for low (distal) vaginal confluence
  - posterior walls of the sinus and vagina opened, but the anterior wall of the vagina is left intact
  - posterior perineal flap is placed into opened vagina
  - widely opens UGS
- pull-through vaginoplasty: for very high vaginal confluence
  - vagina separated from UGS, and sinus used to create a urethra
  - mobilized vagina may reach urethra
    - usually requires skin flaps to do so
- complete vaginal replacement: only for rudimentary or absent vagina

### Describe the operative technique for UGS sinus repair.

- Pre-op
  - ensure pt stable: esp w/ CAH
  - enema for all pts
  - complete bowel prep if needed
  - pre-op antibiotics
  - endoscopy
  - Fogarty catheter left in vagina
  - Foley catheter anchored in bladder

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- prep entire lower body: allows for supine or prone position
- Low vaginal confluence
  - Clitoroplasty
    - traction suture in glans
    - parallel lines on either side of ventral mucosal strip from around the meatus towards the glans and around corona
    - perineal inverted U flap outlined, w/ base extending to either ischial tuberosity
    - Y incision line drawn around the inferior aspect of each labia majora
    - penis degloved, leaving ventral strip
    - longitudinal incisions made through Buck's from glans to bifurcation
      - ◆ exposes cavernosae, which is dissected from the tunics
    - phallic skin split, as in Byars' flaps
    - glans secured to corporal stumps
  - Flap Vaginoplasty
    - U flap incised
    - posterior wall of sinus and vagina dissected free from rectum
    - posterior wall of sinus opened in midline, extended proximally into the posterior wall of vagina
    - sutures placed through perineal flap and then split posterior wall of the vagina and tied
  - Labial reconstruction
    - created w/ split preputial skin
      - ◆ moved inferiorly and anastomosed to preserved ventral plate and lateral vaginal wall
    - Y incision around the inferior aspect of each labia majora is made
    - labia mobilized and secured inferiorly alongside the vagina as a Y-V plasty
- High vaginal confluence
  - perineal inverted U flap incision as previous
  - flap retracted posteriorly
  - dissection in midline b/w posterior wall of sinus/vagina and rectum
  - entire length of the sinus divided in midline posterior to normal caliber of vagina
  - dissect vagina from urethra
  - create urethra from tubularization of sinus
    - closed in 2-3 layers over Foley
  - anterior wall of vagina mobilized inferiorly
  - buttocks flap or laterally based skin flap can be used
  - posterior flap anastomosed to vagina as previous
  - lsbioplasty as previous

### What is involved in a total urogenital mobilization?

- entire sinus is dissected circumferentially and mobilized towards the perineum
- mobilized sinus used to provide a mucosa-lined vestibule or Passerini flap to cover the anterior vaginal wall when a pull-through procedure is done
- allows the midlevel confluence to reach the perineum w/o requiring vaginal separation
- inverted U-shaped perineal flap created as per standard vaginoplasty
  - meatus is circumcised
- initial dissection carried out in the midline posteriorly to peritoneal reflection
- anterior wall mobilized from the phallus
- Fogarty balloon palpable in the vagina
- posterior wall of vagina opened b/w stay sutures
- if vagina near perineum, a flap vaginoplasty easily performed
- if vagina high, anterior wall of vagina separated from urethra and BN
- opening in urethra closed in 2 layers
- mobilized sinus split anteriorly and used as a Passerini flap to create anterior vaginal wall
- posterior perineal flap approximated to the spatulated posterior vaginal wall
- labioplasty as previous

### What are the results of UGS and intersex surgery?

- good cosmetic and early functional results
- failures from failure to exteriorize the vagina initially or from scar formation
- less favourable outcome when initial procedure done before 1 yr of age

### What is involved in the management of a cloacal malformation?

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- Initial management
  - stabilization: child often ill w/ abdo distension, respiratory compromise
  - do not do only rectal pull-through operation at this time: must repair everything in 1 stage
- Decompression of GI tract
  - colostomy: best location controversial
    - divided transverse colostomy: preserves L colic blood supply
    - descending colostomy: less resorption of urine
  - endoscopy at time of colostomy
    - cystoscope tends to enter vagina: entrance into bladder may be difficult
    - leave tubes in all channels for later radiology
- Decompression of GU tract
  - voiding continues into vagina, compressing BN → manage w/ CIC
  - vesicostomy if CIC difficult
- Repair of obstructive GU pathology
  - repair obstructive lesions
- Repair of cloacal malformation
  - usually carried out at 6-12 mo
  - PSARVUP (posterior sagittal anorectovaginourethroplasty)

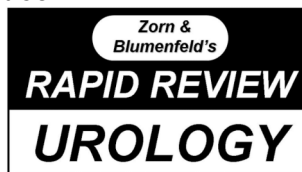
### Describe the operative technique for cloacal repair.

- Preop
  - bowel prep
- Procedure
  - endoscopy
  - Foley in bladder
  - prone position, jackknife
  - electrical stimulation for area of maximal contraction: mark for rectal placement
  - initial incision from tip of coccyx in midline to posterior aspect of cloacal orifice
    - entire dissection in midline until mobilization of rectum and vagina is begun
  - when rectal fistula identified, open posteriorly and place stay sutures
    - better to enter vagina than either the rectum or urethra
  - after rectal mobilization completed, retract away from GU structures
  - mobilization of the vagina(s)
    - avoid devascularization during dissection
    - vaginal bowel interposition segment may be needed if high vagina or vaginal agenesis
  - close the openings in the common cloacal channel w/ 2-3 layers w/ absorbable suture to create a urethra
  - perineal body reconstructed, and rectum is pulled through to perineum
- Post-op
  - monitor GU tract and voiding dynamics
    - poor emptying in 1/3: may need CIC
  - large % have neuropathic UI

### What factors predict continence in the pt after cloacal surgery?

- good perineal raphe
- well-defined anal dimple
- normal spine
- normal MRI
- brisk muscle reflex





## Chapter 70

### • Pediatric Urologic Oncology •

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#### **What is the most common malignant tumour of infancy?**

- neuroblastoma – 8-10% of all childhood cancers
  - most common extracranial solid tumour of children

#### **What is the cellular origin of neuroblastoma?**

- arises from cells of neural crest that form the adrenal medulla and sympathetic ganglia
  - occur anywhere along the sympathetic chain w/ neck, thorax, retroperitoneum, pelvis, or adrenal
  - retroperitoneum 75%, adrenal 50%, paravertebral ganglia 25%

#### **What are the genetics of neuroblastoma?**

- some familial cases: AD pattern
  - risk in sibling or offspring of a pt w/ neuroblastoma: < 6%
  - median age of dx: 21mo, 9mo if familial
- **deletion of the short arm of chromosome 1** in 70-80% of neuroblastomas → is a poor prognostic factor
- **amplification of N-myc** is poor prognostic factor

#### **What is meant by *in situ* neuroblastoma?**

- small nodules of neuroblastoma cells found incidentally in adrenal, at 40-45X greater incidence than clinical tumours
  - histologically indistinguishable from neuroblastoma
  - felt to be regressing spontaneously in most cases

#### **How does one grade neuroblastoma?**

- Shimada classification (1984) – age-linked histopathologic classification
  - subtypes
    - neuroblastoma
    - ganglioneuroblastoma
    - ganglioneuroma = benign differentiated neuroblastoma
  - stroma
    - stroma-poor → if unfavourable histologic features, very poor prognosis (<10% survival)
    - stroma-rich
      - ◆ nodular
      - ◆ intermixed – higher rate of survival
      - ◆ well-differentiated – higher rate of survival

#### **What is the clinical presentation and pattern of spread of neuroblastoma?**

- abdo pain
- palpable mass that crosses the midline
- sx of retention and constipation: due to extrinsic compression of bowel and bladder
- sx of mets: bone/joint pain, periorbital ecchymosis, cough due to lung mets, cord compression
  - mets present in 70% of pts at diagnosis

#### **What unique paraneoplastic syndromes are often seen in pts w/ neuroblastoma?**

- catecholamine release (mimics pheo): htn, palpitation, flushing, headache
- VIP release: watery diarrhea and hypokalemia
- acute myoclonic encephalopathy: myoclonus, opsoclonus (rapid multidirectional eye movements), and ataxia
  - due to Ab against neuroblastoma cross-reacting w/ normal neural tissue
  - treat w/ ACTH, high-dose gamma-globulin, or cyclophosphamide

#### **How can one diagnose neuroblastoma?**

- Labs

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- urinary catecholamines, VMA, HVA all increased in > 90%
- CBC and bone marrow: anemia
- Imaging
  - bone scan + skeletal survey: bone mets in long bones and skull
  - MIBG scan (metaiodobenzylguanidine): taken up by adrenergic secretory vesicles of the tumour cells
- Screening
  - increased screening in Japan

### How does one stage neuroblastoma?

- International Neuroblastoma Staging System (INSS)
  - Stage 1: localized tumour, complete excision +/- microscopic residual disease, -ve ipsilateral LN
  - Stage 2a: localized tumour, **incomplete excision**, -ve ipsilateral LN
  - Stage 2b: localized tumour, +/- complete excision, **+ve ipsilateral LN**
  - Stage 3: **unresectable** cancer crossing the midline, +/- ipsilateral LN involved
    - or: localized unilateral cancer w/ +ve contralateral LN
    - or: midline tumour w/ bilateral extension by infiltration or LN involvement
  - Stage 4: **distant +ve LN**, bone, bone marrow, liver, skin, other organs
  - Stage 4S: localized primary tumour, dissemination to skin, liver, marrow (<10% of tumour) **and < 1 year of age**

### What prognostic factors are present in neuroblastoma?

- Clinical
  - age: children aged < 1 year have improved survival
  - site of origin: better survival for nonadrenal primary tumours
  - stage of disease
    - all stage 1 pts w/ complete resection survive
    - stage 3-4 have poorer prognosis
    - stage 4S: good prognosis, many undergo spontaneous regression
- Biologic variables
  - **N-myc amplification**: associated w/ rapid tumour progression and poor prognosis
  - DNA ploidy: diploid/tetraploid have decreased survival
  - expression of TRKA proto-oncogene (encodes high-affinity NGF receptor) and low-affinity NGF receptor: favourable predictors
  - lack of expression of CD44 glycoprotein on cell surface, serum neuron-specific enolase, serum LDH → all adverse predictors
  - DNA index of > 1.0: favourable

### How can one stratify pts w/ neuroblastoma into specific risk groups?

- Low
  - Stage 1
  - Stage 2a or 2b: < 1yr old, N-myc non-amplified, or favourable histology
  - Stage 4S: < 1yr, N-myc non-amplified, DNA index > 1, and favourable histology
- Intermediate
  - Stage 3: < 1yr + N-myc non-amplified, or > 1 yr + N-myc non-amplified + favourable histology
  - Stage 4: < 1yr + N-myc non-amplified
  - Stage 4S: < 1yr, N-myc non-amplified, DNA index 1.0 or unfavourable histology
- High
  - Stage 2a or 2b: > 1yr, N-myc amplified and unfavourable histology
  - Stage 3: amplified N-myc or unfavourable histology
  - Stage 4S: with amplified N-myc

### What is the treatment for neuroblastoma?

- surgery, chemo, and radiation
  - role of each depends on stage, age, and biologic factors
- Low-intermediate risk disease (Stage I, II, IV-S)
  - Stage 1
    - surgical excision alone: > 90% survival
    - chemo only if recurrence, unless N-myc amplification and unfavourable histology (high risk)
    - no role for radiation
  - Stage 2a, 2b, 3
    - all pts w/ 2a, all infants w/ 2b/3 disease: surgical excision + post-op chemo

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- ◆ no radical resection involving removal of normal organs (esp kidney)
  - radiation only for pts w/ no response to primary or secondary chemotherapy
- Stage 4S
  - resection of the primary is not mandatory: usually have favourable markers
  - if adverse markers, disease is progressive and fatal → aggressive tx w/ high-risk treatment
- High-risk disease
  - extent of resection needed is controversial
  - safest approach: initial chemotherapy, resection post-chemo (decreased risk of rupture)
    - surgery usually 13-18 weeks after initiate chemo (3-4 courses)
    - **relapse is a major problem: 4yr OS 20%**
  - marrow-ablative chemotherapy w/ ABMT
    - tumour debulking w/ surgery or radiation before ABMT
  - <sup>131</sup>I-MIBG
  - ?intraoperative radiation therapy: allows for higher dose of radiation to operative field while sparing N tissues

### Why is tumour resection for neuroblastoma safer after initial chemo?

- decreased risk of tumour rupture
  - tumours are smaller, firmer, less risk of hemorrhage, decreased rate of complications (esp. nephrectomy)

### What is the specific complication to watch for after resection of extensive tumour surrounding the celiac axis and SMA?

- diarrhea: due to resection of autonomic nerves to the gut

### What is the most common soft tissue sarcoma in children?

- rhabdomyosarcoma
  - 15% of all pediatric solid tumours
  - 15-20% arise from GU system
  - bimodal age distribution: peaks at age 2 and adolescence

### What are the most common GU sites for RMS?

- prostate, bladder, paratestis
- vagina and uterus are unusual

### What subgroups of children are predisposed to GU RMS?

- Li-Fraumeni syndrome
  - childhood sarcoma associated w/ mothers w/ excess of premenopausal breast ca + sibs w/ increased risk of ca
  - p53 mutation
- neurofibromatosis

### What cytogenetic abnormalities have been seen in GU RMS?

- embryonal RMS: LOH on 11p15 (not same location of WT2)
- alveolar RMS: translocation b/w 1 or 2 and 13

### How can one classify the histologic variants of GU RMS?

- Intergroup RMS Study Group (IRSG)
  - **embryonal RMS**: most common, better prognosis
    - solid form: arises in muscles of trunk/extremities
    - sarcoma botryoides: polypoid, in hollow organs (bladder, vagina) → excellent survival rate
  - **alveolar RMS**: 2<sup>nd</sup> most common, tends to occur in trunk and limbs - worse prognosis
    - higher rate of recurrence and spread
  - **undifferentiated RMS**: do poorly
  - **pleomorphic RMS** (anaplastic variant of embryonal or alveolar)

### How does one stage GU RMS?

- Intergroup TGNM staging
- T stage
  - Stage 1: favourable site, no mets
  - Stage 2: unfavourable site, small -ve LN, no mets
  - Stage 3: unfavourable site, large or +ve LN, no mets
  - Stage 4: mets



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- Grade
  - G1: favourable histology: embryonal, botryoid, spindle-cell
  - G2: unfavourable histology: alveolar, undifferentiated
- Nodes
  - N0: regional LN not involved
  - N1: regional LN clinically involved
- Mets
  - M0: no distant mets
  - M1site: mets (usually to lungs)

### What factor is most predictive of clinical outcome in RMS?

- tumour stage at diagnosis

### What is the clinical grouping of GU RMS?

- Group I: localized disease completely resected, confined to organ of origin
- Group II: gross resection w/ regional spread, microscopic residual disease, or +ve LN
- Group III: incomplete resection, or after biopsy
- Group IV: distant mets at dx, or +ve cytology in CSF, pleural or peritoneal fluid

### What are the sx of GU RMS?

- depends on site of origin
  - bladder and prostate: obstruction, LUTS, hematuria, abdo mass
    - prostate: solid mass
    - bladder: botryoid form
  - paratesticular: painless scrotal swelling
  - vaginal/vulvar: vaginal bleeding, discharge, vaginal mass → vaginal and paratesticular RMS detected earlier
  - cervix: vaginal bleed/mass
  - uterus: abdominal mass, vaginal bleeding, abdominal mass

### What is the pre-operative evaluation for GU RMS?

- workup of primary: US, CT, or MRI
- metastatic workup: CXR, LFT, bone scan, bone marrow biopsy
- cystoscopy and biopsy for bladder/prostate
- vaginoscopy and biopsy for vaginal, plus above
- D&C for uterine, plus above

### What is the treatment of GU RMS?

- management moving away from exenterative surgery to initial biopsy, chemo, then surgery → preserve pelvic organs
- bladder/prostate: partial cystectomy initially or after chemotherapy
  - radical cystectomy if chemotherapy does not result in adequate shrinkage for partial resection
    - trigone and prostate not amenable to partial or local resection
  - radical prostatectomy if persistent disease or local relapse
- paratesticular: radical orchiectomy + chemo → 90% survival
  - > 90% are embryonal, w/ good prognosis
- vaginal and vulvar: chemotherapy + surgery
- uterine:

### What are the results of treatment of GU RMS?

- bladder salvage rate has increased
  - 60% retain functional bladder at 4 yrs
  - OS > 85%

### What is the role of RPLND in pts w/ paratesticular RMS?

- controversial
  - children < 10 yrs: undergo RPLND
  - children > 10 yrs: ipsilateral RPLND prior to chemo vs. more intense chemo and radiation (sparing them RPLND)
    - 50% chance of having +ve LN
    - radiation required to prevent recurrence and spread

### What is the most common primary malignant renal tumour of childhood?

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- Wilms' tumour (a.k.a. nephroblastoma)

### **What is the mean age of dx for Wilms'?**

- earlier in boys
  - unilateral: 41.5mo (M), 46.9mo (F)
  - bilateral: 29.5mo (M), 32.6mo (F)

### **What is the embryologic origin of Wilms' tumour?**

- develops from remnants of immature kidney

### **What epidemiologic variations are present in Wilms'?**

- incidence lower in East Asian, higher in black populations

### **What anomalies are associated w/ Wilms' tumour?**

- GU anomalies
  - hypospadias: 13%
  - renal fusion anomalies: horseshoe kidney (7X increase)
  - cryptorchidism: 37%
- Denys-Drash association (DDS)
  - male pseudohermaphroditism (MGD)
  - renal mesangial sclerosis
  - Wilms' tumour
- WAGR anomaly – 50% of WAGR w/ chromosome 11 deletion develop Wilms'
  - Wilms' tumour
  - aniridia (1%): 1/3 of pts w/ aniridia get Wilms'
  - genital anomalies
  - mental retardation
- hemihypertrophy / Beckwith-Wiedemann syndrome (BWS): 0.8%
  - macroglossia
  - nephromegaly
  - hepatomegaly
  - hemihypertrophy: 34%

### **What chromosomes have been associated w/ Wilms' tumour?**

- WT1
  - 11p13: tumour suppressor gene
  - regulates transcription of other genes
  - > 90% of DDS pts have germ line deletions in 1 WT1 allele
  - seen in WAGR
- WT2
  - 11p15: linked to BWS
- loss of 16q: in 20% of Wilms'
- loss of 1p: in 10% of Wilms'
  - related to tumour progression rather than initiation
- 7p mutations
- p53 mutation
- 19q13 – familial Wilms' tumour: AD trait w/ incomplete penetrance

### **What pathologic markers are associated w/ unfavourable outcome in Wilms'?**

- nuclear atypia
- sarcomatous tumours (rhabdoid and clear cell types)
- anaplastic Wilms' tumour
  - rarely seen in pts < 2 yrs
  - incidence of 13% in > 5yrs
  - major indicator of poor outcome

### **What are the classic pathologic findings in Wilms' tumour?**

- Gross
  - compresses adjacent normal renal parenchyma: forms pseudocapsule
  - soft and friable

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- necrotic or hemorrhagic areas
- unicentric in 93%, multicentric unilateral in 7%
- Micro
  - expresses variety of cell types found in normal developing kidney
  - may contain skeletal muscle, cartilage, squamous epithelium
  - compact undifferentiated blastema
  - variable epithelial differentiation in the form of embryonic tubules, rosettes, and glomeruloid structures
    - triphasic composition

### What pathologic markers are associated w/ favourable outcome in Wilms'?

- classic (triphasic) composition: blastemal, epithelial, stromal elements
  - worse w/ more blastemal (?stromal) elements

### What histologic abnormalities characterize anaplastic Wilms'?

- nuclear enlargement
- hyperchromasia of enlarged nuclei
- abnormal mitotic figures

### What is the response of anaplastic Wilms' to chemotherapy?

- associated w/ resistance to chemo

### What are *nephrogenic rests*?

- small foci of persistent embryonal cells within otherwise normal kidney tissue
- this term is used for all Wilms' tumour precursor lesions
  - multiple rests = nephroblastomatosis
  - pts w/ nephroblastomatosis need biopsy, chemo, and follow-up imaging rather than aggressive resection
- spectrum of appearances
  - may produce mass that appears like small tumour
  - must do excisional biopsy

### How can one classify nephrogenic rests, and what is the significance of this?

- classified according to relative position within the lobe
  - perilobar (PLNRs): elaborated late in embryogenesis
    - usually seen in pts w/ BWS, linked to 11p15
  - intralobar (ILNRs): due to earlier gestational aberrations
    - seen in WAGR, DDS, linked to 11p13
- direct reflection of chronology of the embryologic development of the kidney
- if < 1yr, dx w/ Wilms', and have nephrogenic rests (esp. PLNRs), **increased risk of contralateral disease**
  - more frequent surveillance for years

### What are the sx of Wilms' tumour?

- mass (>90%), abdominal pain
  - most common initial presentation is an asymptomatic abdominal mass
- hematuria, fever
- rupture of Wilms' → acute abdomen
- extension into IVC: varicocele, hepatomegaly, CHF (<10%)
- production of bioactive substances
  - htn from increased renin in 25%
- signs of associated syndromes: WAGR, BWS, GU abnormalities

### What is needed for the evaluation of Wilms'?

- Labs: CBC, lytes, Cr, LFTs, Ca profile, urinalysis
  - acquired vWD in 8%
  - increased Ca in CMN and RTK
- Imaging: **precise dx cannot be obtained on the basis of preoperative imaging**
  - CXR
  - US: examine IVC to look for thrombus, also to look at contralateral kidney
  - MRI: if US +ve for IVC thrombus
  - CT abdo: both CT and MR are better at assessing contralateral kidney for nephrogenic rests or tumour
  - PET scan

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- CT chest: lung is most common site for distant mets
- skeletal survey and bone scan for bony mets
- head CT/MR if suspect brain mets

### How often does bilateral disease occur in Wilms'?

- 5-7%: often not seen on imaging

### What is the staging system for Wilms' tumour?

- NWTSG
  - Stage I: limited to kidney, vessels not involved, completely excised, no biopsy (FNA excluded) (42%)
  - Stage II: extends through capsule, completely excised (28%)
    - +/- local spillage (not into peritoneum), **previous biopsy**, IVC/renal vein thrombus, extensive renal sinus invasion
    - IVC involvement in 6%
  - Stage III: residual mass in abdomen, +ve LN, diffuse spillage, peritoneal seeding or invasion through peritoneum, or +ve margins (22%)
  - Stage IV: hematogenous mets to lung, liver, bone, brain, or other organ, or distant LN mets (9%)
  - Stage V: bilateral renal involvement at diagnosis

### What are the most important determinants of outcome in children w/ Wilms'?

- histopathology
- tumour stage

### What prognostic factors are important in outcome in Wilms', other than histology and stage?

- chromosomal abnormalities: LOH for 16q
- DNA content
- cytokines: lung mets more common in VEGF-positive tumours
- tumour markers: HA, FGF, plasma renin

### What is the treatment for Wilms' tumour?

- initial treatment: transperitoneal radical nephrectomy
  - emergency OR only for active bleeding or tumour rupture
  - exploration to document extension, mets, peritoneal seeding
  - exploration of contralateral kidney: kidney palpated, inspected on all surfaces, palpate renal vein for thrombus
    - biopsy all suspicious areas
  - avoid tumour spillage: 6X increase in local abdominal relapse
  - no benefit in performing formal LND
- NWTSG V Protocol
  - Stage I-II FH, stage I anaplasia: dactinomycin + vincristine (VD) x 18 weeks → 90% cure rate
  - Stage III-IV FH, stage II-IV focal anaplasia: 10.8 Gy to abdomen, dactinomycin + vincristine + doxorubicin (VAD) x 24 wks
    - cyclophosphamide does not help Stage IV/FH, 10.8Gy same as 20Gy
    - Stage IV FH: radiation based on abdominal stage, + 12Gy to lungs
  - Stage II-IV diffuse anaplasia or stage I-IV clear cell sarcoma: 10.8 Gy to abdomen + 12 Gy to lungs, dactinomycin + vincristine + doxorubicin + cyclophosphamide + etoposide (VAD + EC)
  - Stage I-IV rhabdoid tumour (regimen RTK): radiation, carboplatin + etoposide + cyclophosphamide

### What are the RF for local recurrence of Wilms' tumour?

- tumour spillage: 6X increase in local abdominal relapse
- unfavourable histology
- incomplete tumour removal
- no LN sampling
  - **2 yr survival after local recurrence: 43%**

### What is the role for preoperative chemotherapy in Wilms'?

- benefit in pts with:
  - bilateral involvement
    - bilateral in 5%
    - tx all pts w/ bilateral disease w/ initial bx + neoadjuvant chemo
  - inoperable disease at primary exploration

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- pt tx w/ stage III chemo regimen
- resection completed within 6 weeks after starting therapy
- IVC extension above hepatic veins

### What is the definition of an inoperable tumour in Wilms'?

- determine unresectability at OR
  - preoperative imaging unreliable: tumours can compress without invasion

### What is the treatment for stage V (bilateral disease) Wilms'?

- initial bilateral biopsy: do not excise tumour at initial operation
  - confirm Wilms'
  - define histologic type
- preoperative chemotherapy
- 2<sup>nd</sup> look OR at 8-10 weeks
  - partial nephrectomies or wedge excisions → enucleations will leave residual tumours
  - if extensive tumour prevents excision, complete excision from least involved kidney
  - bilateral nephrectomy + IHD if tumours fail to respond to chemo and radiation
- post-operative re-imaging w/ consideration for further resection

### What are the indications for partial nephrectomy in Wilms' tumour?

- bilateral disease
- solitary kidney
- renal failure
  - only 0.25% of pts develop renal failure after nephrectomy for unilateral tumours (most were DDS pts)
  - pts w/ WAGR at increased risk of renal failure
- pts w/ increased incidence of nephrogenic rests: BWS, hemihypertrophy, aniridia

### What are the late effects of treatment in Wilms'?

- Radiation
  - MSK problems
  - hypogonadism
  - azoospermia
  - adverse prognostic outcome
  - 2<sup>nd</sup> neoplasm: HCC
- Anthracyclines
  - cardiotoxicity: CHF

### What is the DDX of renal tumours in children?

- congenital mesoblastic nephroma : most common renal tumour in infants
  - mean age of dx: 3.5 mo
- Wilms' tumour
- clear cell sarcoma of the kidney
- rhabdoid tumour of the kidney
- solitary multilocular cyst
- cystic partially differentiated nephroblastoma
- metanephric adenofibroma
- RCC
- AML
- TCC
- fibroepithelial polyp

### What is the histologic appearance of CCSK?

- cellular lesion of polygonal cells w/ round oval nuclei
- delicate chromatin pattern w/ indistinct nucleoli

### What are the predictors of improved survival in CCSK?

- lower stage
- younger age at dx
- tx w/ DOX
- absence of tumour necrosis

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### What is the difference b/w Wilms' and clear cell sarcoma of the kidney in terms of mets?

- CCSK associated w/ bone and brain mets → require skeletal survey and bone scan

### What is the most aggressive and lethal childhood renal tumour?

- rhabdoid tumour of the kidney (RTK)
  - 2% of renal tumours

### What are the typical features of rhabdoid tumour?

- Clinical
  - early age at diagnosis
  - resistance to chemo
  - high mortality (80%)
  - brain mets and independent CNS tumours
- Histologic
  - large uniform cells w/ ++ acidophilic cytoplasm
  - discrete zone of pale eosinophilia
  - occur in renal and extrarenal locations

### What is the most common renal tumour in infants?

- congenital mesoblastic nephroma: mean age of dx of 3.5mo

### What are the typical features of CMN?

- Clinical
  - associated w/ polyhydramnios
  - renal mass in young child w/ hypercalcemia
    - N/V, anorexia, constipation, polyuria
  - excellent outcome w/ surgery only
- Histologic
  - firm tumour, yellow-gray, trabeculated
  - local infiltration into surrounding perirenal CT
  - no pseudocapsule like in Wilms'
  - composed of bundles of spindle cells

### What are the typical features of solitary multilocular cyst?

- Clinical
  - 50% in young children, usually boys
  - also seen in young adult women
- Histologic
  - all are unilateral
  - well-encapsulated multilocular tumour composed of cysts compressing renal parenchyma

### What are the typical features of RCC in children?

- Clinical
  - abdominal mass (most common)
  - hematuria

### How can one classify prepubertal testicular tumours?

- Germ cell tumours
  - yolk sac
  - teratoma
  - mixed
  - seminoma
- Gonadal stromal tumours
  - Leydig cell
  - Sertoli cell
  - Juvenile granulosa cell
  - mixed
- Gonadoblastoma
- Tumours of supporting tissues

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- fibroma
- leiomyoma
- hemangioma
- Lymphomas and leukemias
- Tumour-like lesions
- Secondary tumours
- Tumours of the adnexa

### **What % of prepubertal testicular tumours are germ cell?**

- 65%

### **What chromosomes have been implicated in adolescent and adult germ cell tumours?**

- loss of chromosome 11, 13, 18
- gain of chromosome 7, 8, X
- isochromosome of 12p, or i(12p) → 2 copies of 12p
  - most infantile testicular endodermal sinus tumours are diploid or tetraploid, while adult tumours are aneuploid

### **What are the other names that yolk sac tumour is known by?**

- endodermal sinus tumour
- embryonal adenocarcinoma
- infantile adenocarcinoma of the testis
- orchidoblastoma
- Teilmann's tumour

### **What are Schiller-Duval bodies?**

- characteristic histologic findings in YST
  - similar to endodermal sinuses seen in rat placenta

### **What is the pathognomonic histologic feature of Leydig cell tumours?**

- Reinke's crystals
  - present in only 40% of tumours
- also have abundant eosinophilic cytoplasm

### **What are the sx of testicular tumours in children?**

- painless testicular mass
- abdominal pain: if torsion

### **What is the management of testis CIS in kids?**

- repeat bx after puberty in prepubertal pts w/ CIS

### **How does one stage testicular germ cell tumours in children?**

- Children's Oncology Group staging system: based on tumour markers and pathologic findings
  - Stage I: tumour limited to testis, markers –ve after orchiectomy
  - Stage II: microscopic residual disease in scrotum or cord, markers remain elevated, tumour rupture/biopsy
  - Stage III: retroperitoneal LN +ve
  - Stage IV: distant mets

### **Why must tumour markers be interpreted differently in children for testis tumours?**

- increased AFP after orchiectomy does not always represent residual disease
  - AFP synthesis continues after birth (by fetal yolk sac, liver, and GI tract)
  - normal adult levels not reached until 8 months
  - hCG levels rarely increased in preadolescent tumours

### **What is the typical behaviour of teratoma in children?**

- Mature: prepubertal mature teratoma has a benign clinical course
- Immature: appear to be benign unless they have foci of malignancy
  - observation alone for completely resected immature teratoma

### **What is the most common prepubertal testicular tumour of germ cell origin?**

- YST: 60% of all tumours

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→ usually in kids < 2yrs

### **What is the incidence of mets in YST?**

- mets to retroperitoneal LN in 4-6%
- most common site of distant mets is lung (20%)

### **What is the treatment for YST in children?**

- Stage I
  - inguinal orchiectomy
  - RPLND and chemo not indicated routinely
  - no adjuvant tx after orchiectomy
  - CXR, CT/MRI abdomen qmonth x 3mo, again 3mo later, then q6mo until 3 yrs
  - tumour markers and exam more frequently: 90% of YST make AFP
- Stage II
  - completion orchiectomy w/ removal of all cord structures
  - abdo CT, LN biopsy if enlarged: BEP chemo if +ve
- Stage III
  - chemo w/ platinum-based drugs
  - surgery at 3mo if enlarged nodes or elevated markers after chemo

### **What are the most common nongermlinal testicular tumours in children?**

- gonadal sex-cord stromal tumours
  - are able to secrete hormones

### **What is the differential diagnosis of precocious puberty?**

- pituitary lesions
- Leydig cell hyperplasia
- Sertoli cell tumours
- hyperplastic testicular nodules

### **What are the most common sex-cord tumours?**

- Leydig cell tumour: most common
  - peak incidence 4-5y
  - produces T: results in precocious puberty
- Sertoli cell tumour: 2<sup>nd</sup> most common
  - incidence earlier than Leydig
  - present as painless testicular mass, gynecomastia

### **What treatment is required for Leydig cell tumour?**

- inguinal orchiectomy only
  - malignancy not reported

### **What is the treatment for Sertoli cell tumour?**

- observation in infants, orchiectomy in others

### **What is the natural history of gonadoblastoma?**

- occur in dysgenetic gonads, associated w/ presence of Y chromosome
  - MGD: 25% risk of gonadoblastoma, incidence increases w/ age
- germ cell component of gonadoblastoma is prone to malignant degeneration into sem and nonsem tumours
- streak gonads in pts w/ gonadal dysgenesis should be removed

### **What is the treatment for gonadoblastoma?**

- early gonadectomy: tumours have been reported in children < 5yrs

### **What are the most common malignancies to spread to the testicle in children?**

- leukemia and lymphoma
  - ALL: 20% incidence of testicular relapse
  - testicular involvement in 4% of kids w/ Burkitt's lymphoma

### **What is the major difference in how GU tumours behave in children compared to adults?**



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- most pediatric tumors are very sensitive to chemo and radiation  
→ think of all tumours like testis cancer

### **What is the false –ve rate of imaging for Wilms' tumour?**

- 7%

### **What is the definition of favourable pathology in Wilms'?**

- lack of diffuse anaplasia

### **How does diffuse anaplasia on biopsy affect future treatment of Wilms'?**

- contraindication to subsequent renal-sparing surgery

### **What was the goal of NWTs V, and why was the trial closed?**

- proposed to eliminate chemo for stage I Wilms' < 2 yrs of age w/ tumour < 550g in size
- closed due to a high # of relapse
- **there are no Wilms' tumours that should not receive chemo**

### **Why is partial nephrectomy not recommended for congenital mesoblastic nephroma?**

- CMN is not encapsulated

### **What is the effect of 13-cis-retinoic acid in pts w/ stage IV neuroblastoma?**

- causes normal differentiation of neuroblastoma cells in culture
- combination chemo, whole-body rads, and ABMT improved w/ addition of 13-cis-retinoic acid

### **What is the natural history of RMS?**

- rapid growth and invasion w/ hematogenous mets to regional LN
- w/ pts develop mets, 80% do so within 1 yr of diagnosis

### **What is the classic triad of findings in Leydig cell tumour?**

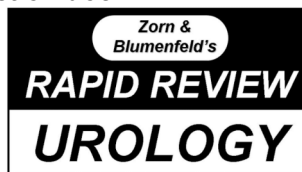
- precocious puberty
- unilateral testis mass
- elevated 17-ketosteroids

### **What are the possible complications of treatment for childhood GU malignancy?**

- secondary malignancy
  - renal failure
    - due to radiation
    - due to nephrectomy
    - nephrotoxic chemo
  - hypogonadism
  - infertility
- hemorrhagic cystitis

### Recommendations:

- **Advances in Pediatric Urologic Oncology – AUA Update XXII #4**



## **Chapter 71**

### **• Urinary Tract Reconstruction in Children •**

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#### **How does contact of urine w/ bowel affect renal function?**

- urinary solutes (esp Cl<sup>-</sup>) absorbed from urine in contact w/ bowel mucosa (large and small)
- pts w/ decreased renal function may develop metabolic acidosis
  - if acidosis exists preoperatively, will worsen if urine stored in bowel segments
- pts w/ renal failure or other medical problems may develop oliguria
- some medications secreted in urine may be reabsorbed by bowel

#### **How does contact of urine w/ bowel affect GI function?**

- reabsorption of ammonia may be dangerous for pts w/ hepatic failure
- hx of chronic diarrhea or fecal incontinence preop: concern regarding use of ileocecal valve

#### **What is involved in the evaluation and pre-op preparation of the pt for bladder reconstruction?**

- Hx/Px
  - PMHx: renal failure, liver failure, short gut syndrome
  - incontinence/diarrhea
  - must determine commitment of pt and family
    - wait until all needs of pt identified
  - identify pts that may need ACE procedure
- Labs: lytes, BUN, Cr, 24hr urine collection
- Imaging
  - upper tract imaging: r/o VUR if hydro present
  - VCUG
- Urodynamics
  - reconstruction must result in resting pressure of < 40cm H<sub>2</sub>O
  - must consider potential for unmasking hostile bladder by increasing BN or EUS resistance
    - EMG of EUS can be performed
  - assess pts ability to empty bladder
    - no test can predict ability to void and empty after augment or other reconstruction
    - must emphasize need for CIC if necessary
- Pre-op
  - optimize general medical status
  - correct nutritional and hydration abnormalities
  - manage pre-existing CVS and pulmonary problems
  - bowel prep: 2d of CF, full mechanical prep +/- PO antibiotics
    - IV antibiotics or bowel prep not needed for gastrocystoplasty
  - urine C&S
  - cystoscopy/endoscopy

#### **What principles should be followed for TUU?**

- better ureter should be implanted into the bladder, draining the other one across
  - if native bladder too small for 2 reimplants, just do 1 + TUU
- crossing ureter mobilized to swing gently across the abdomen
  - smooth course w/o tension
- mobilize w/ all adventitia to preserve blood supply
- do not angulate beneath IMA
- wide anastomosis
- recipient is not mobilized or brought medially

#### **What principles should be followed for a psoas hitch?**

- new hiatus should be as high on bladder as possible

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- reimplant should be long (8-10cm)
- bladder secured to psoas muscle and fascia w/ nonabsorbable sutures
  - include tendon if present
- sutures must not enter bladder lumen: stones
  - don't tie until all sutures are placed
  - surgeon should hold bladder while assistant ties
- broad shallow purchases of psoas, not too tightly
- contralateral bladder pedicle can be divided to increase bladder mobility
- ureteral reimplant should be done before psoas hitch

### What are the various approaches available for BN reconstruction?

- Injection w/ BN bulking agents
  - don't use GAX-collagen in spina bifida kids: is not latex free
  - limited durability, ++ cost
  - limited role, for select group of pts
- Extrinsic compression
  - AUS
    - can result in prompt continence in kids w/ preservation of ability to void spontaneously
    - place cuff at BN in all girls and prepubertal boys
    - repositioning of cuff not necessary
    - must be able to perform CIC
    - upper tract changes may occur
    - augment may be necessary
  - Sling
    - most pts that get sling must be prepared for CIC
    - augment often performed, as hyperreflexia often overcomes BN resistance to achieve continence
    - higher rate of success w/ circumferential fascial wrap, augment
    - erosion rarely occurs
- Constriction and narrowing procedures
  - Young-Dees-Leadbetter (YDL)
    - Young: excise a portion of BN and tightening remainder over probe
    - Dees: extend length of excised tissue through the trigone
    - Leadbetter: elevate ureters off trigone, place in more cephalic position on bladder floor
      - ◆ allows for tubularization of the trigone and further enhancing of the urethra
  - Mitchell
    - addition of external support w/ placement of silicone sheath around reconstructed BN
      - ◆ protects space for future placement of AUS
- Urethral lengthening procedures (flaps)
  - Tanagho
    - cephalad-based anterior detrusor wall tube
    - closure of tubularized BN created circularly oriented muscle fibers
    - should not be used in the neurogenic population
  - Pippi Salle
    - anterior bladder onlay flap
    - posterior wall of urethra is kept intact: less hangup during CIC
    - less catheterization trouble compared to Kropp, but less continence
  - Kropp
    - urethral lengthening and creation of a flap valve for neurogenic BN and sphincter dysfunction
    - based on an anterior detrusor wall tube that is kept in continuity w/ urethra, tubularized, and implanted into a submucosal tunnel in trigone
    - continence in > 90%
    - some problems w/ catheterization, can have upper tract deterioration or bladder rupture
- BN closure w/ continent catheterizable stoma
  - must use only in pts that can reliably catheterize

### Describe the Kropp surgical technique for urethral lengthening.

- Foley placed, bladder filled
- bladder exposed through midline or low transverse abdominal incision
- 5x1.5cm rectangular flap based on BN and urethra
- flap mobilized in continuity w/ urethra

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- detrusor at BN divided, separating bladder and urethra
- rectangular strip tubularized posteriorly around urethral catheter
- submucosal tunnel created through trigone
- eliminate dead space at entrance of urethra into bladder
- tubularized neourethra long enough to reach the true lumen of bladder

### Describe the Pippi Salle technique for urethral lengthening.

- anterior full thickness bladder wall flap 5x1cm mobilized to BN w/ 1mm of epithelial edges excised to avoid overlapping suture lines
- 2 parallel incisions down to level of muscle made in mucosa of trigone from native BN
- anterior flap secured to midline strip of trigone mucosa to create a tube
- more lateral mucosa of trigone mobilized and closed over midline urethra
- distally, BN muscle is wrapped tightly around urethra w/ closure
- lengthened urethra should extend into bladder

### How does one manage the native bladder in augmentation cystoplasty?

- preserve native bladder as long as it is widely opened
  - sagittal incision to bivalve bladder
    - incision from a pt several cm above trigone to position just above the trigone posteriorly
  - 2<sup>nd</sup> transverse incision to achieve stellate bladder possible

### What are the advantages of detubularization of bowel?

- maximizes volume achieve for surface area
- blunts bowel contractions
  - intact segments can achieve pressures of 60-100cmH<sub>2</sub>O
- improves overall capacity and compliance

### What are the options for bowel segment selection for augmentation cystoplasty?

- ileocystoplasty
  - 20-40cm segment of ileum 15-20cm away from IC valve
  - must have adequate mesentery to reach native bladder w/o tension
  - ileum anastomosed to itself w/ running absorbable, full thickness, inverting mucosa
  - place SP, Foley, drain
- cecoplasty
  - cecum opened and reconfigured, w/ segment of ileum used to reach ureters
- ileocecoplasty
  - ileal segment can be opened and used as patch on cecal segment before augment
  - 15-30cm of terminal ileum used
  - Mainz ileocecoplasty: ileal segment 2X length of cecum, all opened and closed in Z formation
  - appendix useful in creation of continent abdominal wall stoma
    - removed w/ small cuff of cecal wall and tunneled into native bladder, or left in situ
  - **ileocecal valve used less in children: can cause intractable diarrhea**
- sigmoid cystoplasty
  - 15-20cm sigmoid isolated, reconfigured, attached as patch
  - possible to close the 2 ends and open antimesenteric border, or fold in U shape
- gastrocystoplasty
  - antrum
    - L gastroepiploic artery used as a pedicle
    - if R gastroepiploic artery is dominant, strip of body along greater curvature from L gastroepiploic artery is maintained
  - body
    - gastric wedge from midportion of greater curvature used
      - ◆ higher concentration of acid cells
    - R artery commonly dominant, used more
    - incision into stomach stopped just short of lesser curvature to avoid injury to vagus
    - L gastric artery branches ligated
    - stomach incised, native stomach closed in 2 layers
    - segment passed through windows in transverse mesocolon and distal ileum mesentery: not free floating in abdomen
    - if does not reach abdomen, either gastroepiploic artery can be mobilized closer to its origin

**What is involved in the postoperative management of pts w/ augmentation cystoplasty?**

- Early
  - NG until bowel function recovers
  - fluid and electrolyte monitoring
  - SP: irrigate TID or if drainage slows
    - maintain x 3 weeks
  - drains removed quicker in pts w/ VP shunt
  - CIC after SP out
  - check PVR
- Late
  - upper tract surveillance at 6/52, 6/12, 1 yr w/ US
  - lytes, BUN, Cr, cultures q3mo
  - yearly endoscopy

**What are the complications of augmentation cystoplasty?**

- GI
  - bowel obstruction: uncommon (3%)
  - chronic diarrhea: rare
    - more likely if remove IC valve
  - vitamin B<sub>12</sub> deficiency and megaloblastic anemia
  - early satiety
  - disorders of gastric emptying
- Bladder
  - decreased compliance
    - may require secondary augmentation
- Metabolic complications
  - hyperchloremic metabolic acidosis
    - acid absorbed when urine in contact w/ intestinal mucosa
    - tx: bicarbonate
    - jejunum: hyponatremic, hypochloremic, hyperkalemic metabolic acidosis
  - delayed pt growth
  - hypokalemic, hypochloremic, metabolic alkalosis in gastrocystoplasty
  - hematuria-dysuria syndrome
    - almost all pts w/ gastrocystoplasty have hematuria or dysuria w/ CIC or voiding occasionally
      - ◆ granular excoriation
    - usually mild, require no tx
    - tx: H<sub>2</sub>-blockers, PPI if needed, bladder irrigation w/ baking soda
- Mucus
  - can impede bladder drainage, form stones, UTI
  - may increase in presence of cystitis
  - colonic segments make more than ileum
  - need daily irrigations
- UTI
  - use of CIC can increase bacteriuria
  - incidence of pyelo after augment similar to conduit
  - treat bacteriuria if urease-splitting organism: may lead to stone formation
- Stones (18%)
  - usually struvite
  - if stones occur, assess adequacy of emptying
- Tumours
  - usually adenocarcinoma at ureterocolonic anastomotic site
  - require yearly surveillance w/ endoscopy: earliest seen at 4 yrs
- Delayed spontaneous bladder perforation
  - cause unknown
  - usually occur in bowel segment itself: no increased incidence w/ particular type of segment (?sigmoid in Indiana group)
  - Sx: pain, distension, fever, sepsis, N/V, decreased u/o, shoulder tip pain, pelvic masses
  - dx w/ contrast cystography
  - Tx

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- immediate surgical repair
- conservative tx w/ catheter, antibiotics, and abdo exams successful in 87% if no definite rupture

### What are the potential causes for delayed spontaneous bladder perforation?

- trauma to bowel from fixed adhesions that result in shearing forces w/ emptying and filling
- chronic transmural infection
- chronic bowel wall ischemia
  - chronic overdistension
- high outflow resistance causing increased bladder pressure

### What are the issues in pregnancy in women that have undergone augmentation?

- will expanding uterus and fetus affect pedicle?
- is bacteriuria more problematic?
- is C-section necessary?
- will pedicle be damaged during C-section
  - no answers available

### What is the optimal segment to use for augmentation cystoplasty?

- choose based on needs of the particular pt
  - no one segment is superior
- use ileum if no clear advantage
- reserve stomach for kids w/ renal failure and acidosis, short gut, or radiation

### What are the alternatives to GI cystoplasty?

- ureterocystoplasty
  - use refluxing ureter that has massive dilation, draining poorly functioning or nonfunctioning kidney
  - standard nephrectomy
  - bladder opened in sagittal plane
    - avoid branches of superior vesical artery
  - ureter left in continuity w/ bladder, and opened longitudinally, avoiding main blood supply
  - ureter folded in on itself, anastomosed
  - children more likely to void after ureterocystoplasty than intestinal
- autoaugmentation
  - detrusor excised over bladder dome, leaving mucosa intact to protrude as wide mouthed diverticulum
  - lateral edges of detrusor secured to psoas bilaterally
  - limited increase in volume
  - rare perforation
- seromuscular enterocystoplasty
  - circumferential incision around bladder, removing detrusor and preserving mucosa
  - sigmoid segment isolated, and mucosa removed
  - sigmoid segment sewn to bladder muscle
  - drain space b/w bladder mucosa and sigmoid segment
  - more complications: blood loss, OR time, reoperative rate
- bladder regeneration

### What are the options for continent urinary diversion in children?

- ureterosigmoidostomy and its variants
  - significant complications (acidosis, infection, hydro, colon ca) limit its use
  - Mainz II pouch: colon incised along antimesenteric border for 6cm proximal and distal to rectosigmoid junction, ureters implanted, and colon reconfigured and closed
  - Kock colorectal valve: limits amount of colon exposed to urine → decreases acidosis
  - must assess competence of anal sphincter: if incapable of fecal continence w/ diarrhea, cannot use
- nipple valves
- flap valves and Mitrofanoff
  - create submucosal tunnel for supple small-diameter conduit
  - as reservoir fills, increased Pves transmitted to implanted conduit, coapting its lumen
  - most reliable of all continence mechanisms
    - rare incontinence
    - stomal stenosis is common: may require formal revision
  - possible to use ureter, fallopian tubes, gastric tube, or Monti procedure

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- ileocecal valve
  - short segment of ileum used as efferent limb
  - imbricated ileocecal valve
  - Indiana pouch has excellent results
- hydraulic valves
  - Benckroun procedure: urine from reservoir enters sleeve around catheterizable channel
    - compression of inner tube provides continence
    - results not duplicated: procedure abandoned
- continent vesicostomy
  - Yachia: bladder tube fashioned from wide based flap of anterior bladder wall
  - Hanna: continence mechanism based on flap of bladder or intestinal tissue fashioned after prior enterocystoplasty
    - rectangular flap in continuity w/ bladder tubularized
    - bladder plicated around proximal 3cm of tube to create a nipple: like Nissen procedure
  - Macedo continent catheterizable stoma: catheterizable intestinal limb in continuity w/ augmented segment
    - tubularized segment folded onto pouch, buried w/ interrupted sutures
  - Casale continent catheterizable stoma
    - parallel incisions made in bladder dome, creating full-thickness bladder strip
    - epithelium incised for another 2.5cm
    - edges of the epithelium mobilized, allowing for tubularization
    - epithelium, then muscle both tubularized from bladder to tip of string w/ absorbable
    - lateral edges of the epithelium are reapproximated over the tubularized bladder segment w/ absorbable
    - bladder closed

### Describe the surgical technique used to create a Mitrofanoff flap valve.

- low midline or transverse incision
  - allows for adequate mobilization of appendix to bladder
- mobilization of ascending colon along line of Toldt
- base of appendix is amputated leaving small cuff of cecum w/ appendix
- cecum closed
- location selected for implantation of appendix into bladder
  - based on length of appendix, bladder mobility, location for appendiceal stoma
  - usually into posterolateral position in bladder
- base of appendix brought to abdominal wall
  - can be hidden in umbilicus
- keep very short conduit to prevent kinking and problems w/ CIC
- repeatedly catheterize stoma after each step to ensure ease of CIC
  - revise previous step if does not work
- leave 6-10F catheter for 2 weeks

### What is the Monti procedure (aka Yang-Monti)?

- tapered intestinal segment
  - 2cm length of ileum harvested
  - segment opened horizontally and tubularized in longitudinal fashion
  - may change area of incision to create differing lengths of limbs
    - shorter limb for implantation into bladder
    - longer limb for abdominal wall implantation
  - remains short: may not reach skin w/o tension in obese pts
  - can anastomose 2 together for adequate length, or use Casale procedure

### What is the Casale procedure?

- modification of Monti tapered intestinal segment
  - use initial segment that is 2X as long
  - partially split in middle
  - opened on opposite sides to create a longer strip: up to 12cm

### What are the results w/ pediatric continent diversion?

- good results: similar to adults
- high continence rates: 85%
- most common complication: stomal stenosis

## **Chapter 71 Questions - Paeds reconstruction.doc**

### **What is the ACE procedure?**

- antegrade continence enema
  - use appendix for antegrade enemas to control constipation and achieve continence
  - perform OD
  - 25min transit time
  - some kids need catheterization of appendix BID to prevent contracture







## Chapter 72

### • Pediatric Endourology and Laparoscopy •

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**What is the youngest child that may permit a ureteroscope?**

- 4 months  
→ rigid 6.9F ureteroscope may be used

**What are the indications for ureteroscopic intervention in children?**

- limited mostly to stones  
→ children tend to pass stones more readily than adults

**What is the smallest ureteral access sheath that is available?**

- 10F  
→ can be passed into 8-10 year old child

**What are the results of ureteroscopy in children?**

- good efficacy, minimal complications  
→ 90% stone free

**What are the indications for percutaneous renal access in children?**

- stone removal  
→ ESWL failure  
→ anatomy that decreases chance of ESWL success: exstrophy, neurogenic bladder, reconstruction, ureteral reimplant
- ablation of calyceal diverticula, endopyelotomy, ureterotomy

**Describe the procedure of PCNL in children.**

- Pre-op  
→ imaging of GU tract essential  
→ sterilize infected urine  
→ perioperative antibiotics  
→ Foley placed
- Access  
→ may obtain initial access day prior: decreases OR time, blood loss  
→ 24-30F perc access sheaths  
→ irrigation must be warmed: use NS in all cases  
→ most procedures done w/ miniature endoscopes: 7-8F offset cystoscope w/ 5F working channel  
→ access w/ C-arm  
→ pt prone, adequate padding  
→ 22G finder needle from posterolateral position: aspirate urine  
→ contrast via ureteral catheter can be placed  
→ needle lined up to get bullseye and advanced into collecting system  
→ wire advanced into calyx, down ureter  
→ dual lumen catheter placed for 2<sup>nd</sup> wire: safety  
→ 11F pediatric access sheath placed
- Stone Manipulation  
→ small stones removed w/ basket or 3-prong graspers  
→ laser, EHL
- Post-op  
→ leave 6F nephroureterostomy tube

**What are the indications and contraindications for endopyelotomy in children?**

- Indications  
→ not clear  
→ procedure of choice after failed pyeloplasty in the adult: ?same for children

## Chapter 72 Questions - Paeds lap endo.doc

- attempt only if lumen is visible and can be cannulated
- Contraindications
  - large collecting system
  - poor renal function

### Describe the procedure of endopyelotomy in children.

- posterolateral approach through middle calyx
  - ureteroscopic endopyelotomy limited in younger children, due to small ureteral diameter
- posterolateral incision made in UPJ
- stent placed: adult UPJ stents are too big

### What are the indications for diagnostic laparoscopy in children?

- identification of nonpalpable testes
  - presence or absence, location, and anatomy
- intersex states
- hernia

### What are the patterns that may be seen during laparoscopy for nonpalpable testis?

- normal
  - triangular arrangement of vas, lateral gonadal vessels, and iliac vessels
  - obliterated umbilical is seen, vas crosses over towards internal ring
  - vessels course into closed ring
- vanishing testes (16%)
  - vas and vessels dwindle away before internal ring
  - no need to explore if vessels not seen
  - may be necessary to move cecum away
- vessels pass into ring
  - requires inguinal dissection
    - testicular nubbin: 29%
    - testis present: 14%
- intra-abdominal testis (37%)
  - may be "peeping" testis: sits at internal ring
- nondiagnostic: 3% → various causes

### What are the possible findings at diagnostic laparoscopy for intersex conditions?

- palpable gonads, virilized, possible uterus
  - deficiency of MIS → identify and excise mullerian structures
- no palpable gonads, virilized
  - pure gonadal dysgenesis, true hermaphroditism → gonadal bx/removal, define mullerian anatomy
- asymmetry/1 palpable gonad, virilized
  - MGD → evaluate opposite gonad w/ bx, removal
- female
  - male pseudohermaphroditism, AIS, or 5 $\alpha$ -reductase deficiency → gonadectomy or orchiopexy

### What is the role of laparoscopy during hernia repair?

- evaluation of the contralateral inguinal ring
  - pass endoscope through ipsilateral hernia sac after mobilization
  - need 70-90 degree endoscope
  - patent processus evident as gaping passage through the ring
  - if seen to be open, contralateral inguinal exploration performed

### What are the indications for operative laparoscopy in children?

- 1<sup>st</sup> stage Fowler-Stephens
- lap orchidopexy
- evaluation of intersex states
- pediatric lap nephrectomy or partial
- lap ureteral reimplantation (extravesical)
- lap pyeloplasty
- lap autoaugmentation of the bladder

## Chapter 72 Questions - Paeds lap endo.doc

### What are the physiologic changes seen in children during laparoscopy?

- Pulm
  - increased IAP
    - less pressure needed in kids
  - absorption of CO<sub>2</sub> across the peritoneum
    - hypercarbia well tolerated in healthy kids
  - risk of CO<sub>2</sub> embolus
    - sx: increasing ET/CO<sub>2</sub>, decreasing sat, CVS collapse, "mill-wheel" murmur
    - place pt in L decubitus, attempt aspiration of CO<sub>2</sub> through CVP line
  - decreased pulmonary reserve
  - low FRC and lower oxygen reserve
    - decreased ability to withstand decreases of oxygen saturation
  - increased vent pressures: impairs ventilation and gas exchange
- CVS
  - increased preload and afterload and filling volumes
- Temp
  - temperature regulation harder in kids: greater ratio of surface area to body mass: lose heat more quickly
- GU
  - decreased U/O: due to increased IAP
    - transient

### What are the complications of pediatric laparoscopy?

- Complications related to access
  - injury to intraabdominal structures
    - less resistance to penetration, less force needed
    - peritoneum more likely to separate from abdominal wall
  - hernia: must close all 3.5-5mm ports
    - not necessary to close 2mm sites
- Operative complications
  - usual cause is limited working space

### Describe the operative technique for laparoscopic orchidopexy.

- EUA – examination under anesthesia!
- diagnostic laparoscopy
- evaluate testis for size and location
  - vasal/epididymal anomalies or atrophic testis: orchiectomy
  - conversion to 2 stage: if limited by vessels
- place 2 2-3mm ports in anterior axillary line high in the lower umbilical quadrants
- peritoneum incised lateral to gonadal vessels and extended to internal ring
- peritoneum distal to vas is incised
  - leave triangle of undisturbed tissue b/w vas and gonadal vessels
- window created behind the cord from medial to lateral peritoneal dissections
- gubernaculum divided w/ cautery
- incision made above pubic tubercle
- deliver testis to scrotum, perform orchidopexy

### What are the advantages to retroperitoneal laparoscopy in children?

- decreased risk of injury to intraperitoneal organs
- shortest distance to kidney
- less risk of peritoneal contamination
- fewer exposure problems from bowel/liver/spleen covering

### How does one gain access for pediatric percutaneous renal surgery?

- Transperitoneal
  - Nephrectomy
    - initial camera placement: open or closed technique in umbilicus
      - ◆ avoids urachus and obliterated umbilicals
    - 2<sup>nd</sup> cannula placed in ipsilateral lower quadrant
    - 3<sup>rd</sup> cannula above umbilical port, near midline
      - ◆ avoid falciform

## **Chapter 72 Questions - Paeds lap endo.doc**

- NUU
  - inferior port on opposite side, to facilitate mobilization of distal ureter
- Retroperitoneal
  - Prone
    - subcostal incision, muscle splitting
    - enter Gerota's
    - use balloon or finger of surgical glove tied to insufflator to create working space
    - blunt dissection w/ camera
    - 2<sup>nd</sup> and 3<sup>rd</sup> ports placed just above iliac crest
  - Flank
    - small muscle splitting incision off tip of 12<sup>th</sup> rib
    - 2<sup>nd</sup> and 3<sup>rd</sup> ports placed above iliac
    - avoid injury to peritoneum
      - ◆ blunt dissection w/ camera will help

### **What is the critical feature in pediatric partial nephrectomy?**

- delicacy of the renal vasculature in the remnant segment
  - limit mobilization of remnant pole
  - isolate affected vessels close to their renal unit

### **What is the Vecchietti operation?**

- creation of a neovagina in MRKH syndrome
  - olive shaped device placed at vaginal dimple
  - constant upward traction applied transabdominally via sutures brought out through anterior abdominal wall
  - creates neovaginal space in 2 weeks



**Chapter 73**

**• Tissue Engineering Perspectives for Reconstructive Surgery •**

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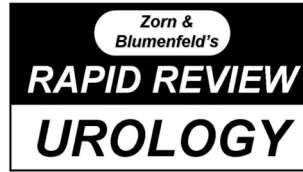
**What are the classes of biomaterials that have been used for engineering of GU tissues?**

- naturally derived materials
  - collagen
  - alginate
- acellular tissue matrices
  - bladder submucosa
  - small intestine submucosa
- synthetic polymers
  - PGA
  - PLA
  - PLGA

**What strategies have been proposed for regeneration of urethral tissue?**

- woven meshes of PGA
- PGA mesh tubes coated w/ polyhydroxybutyric acid (PHB)
- small intestine submucosa (SIS) as onlay patch
- acellular collagen matrix





## Chapter 74

### • Molecular Genetics and Cancer Biology •

#### Define the following terms:

- Allele: One of the various forms of a particular gene at a particular locus on a chromosome.
- Amplification: Additional copies of chromosomal sequence; these sequences may include genes.
- Aneuploid: Deviation in chromosomal number from the usual diploid state.
- Annealing: pairing of 2 single strands of complementary DNA sequences to form double helix.
- Base pair: The physical relationship between adenine/thymidine and guanine/cytosine within the double helix of DNA. Abbreviated as bp, it provides the unit of measurement for DNA.
- cDNA: A segment of DNA complementary to an RNA sequence.
- Chromosome: segment of DNA expressing large # of genes. In humans: 23 such segments.
- Codon: Three sequential nucleotides that represent a particular amino acid or a stop signal.
- Deletion: The removal of a segment of DNA, with rejoining of the outside ends.
- Diploid: A set of chromosomes containing two complete copies of DNA.
- Dominant: Allele determining the expression of a gene.
- Endonuclease: An enzyme that cuts DNA or RNA within the chain.
- Exon: sequence of DNA represented w/ complementary RNA sequence = coding sequence.
- Expression vector: A vector designed to encode a particular DNA sequence or gene for transcription and translation into protein.
- Frameshift mutation: A deletion or insertion of DNA that shifts the normal codons into a different order for translation into protein.
- Gene: segment of DNA that contributes to protein formation, including both introns (noncoding regions) and exons (coding regions) as well as regions preceding and following coding regions.
- Genetic code: correspondence b/w triplets of DNA or RNA (codons) and amino acids making up proteins.
- Genotype: The genetic makeup of an organism.
- Hemizygote: Having only 1 copy of a gene owing, for example, to loss of chromosomal material.
- Heterozygote: Having two different copies (alleles) of a gene.
- Homozygote: Having two identical copies (alleles) of a gene.
- Hybridization: The physical pairing of complementary RNA and DNA.
- Intron: A segment of DNA that is transcribed but is removed by splicing together the exons on either side; part of the noncoding sequences of a gene.
- Karyotype: All the chromosomes within a cell.
- Linkage: tendency for genes near one another on a chromosome to be inherited together.
- Locus: The position of a particular gene on a particular chromosome.
- Methylation: The addition of a methyl group to the nucleotide cytosine; DNA methylation is often associated with decreased transcription of genes.
- Mutation: Any change in the sequence of genomic DNA.
- Northern blotting: A technique of transferring RNA from an agarose gel to a nitrocellulose filter for hybridization with a complementary DNA.
- Oncogenes: Genes that encode for proteins that can transform normal cells into cancerous cells.
- PCR: Polymerase chain reaction, a technique using sequential temperature cycles favoring denaturation, annealing of primer sequences, and extension with DNA polymerase to amplify a large number of copies of a particular sequence of DNA. This technique can be used to detect very small amounts of DNA by creating a huge number of identical copies.
- Phenotype: The appearance or function of an organism, reflecting the contributions of the genotype and the environment.
- Ploidy: The number of copies of chromosomes within a cell; diploid has two copies, triploid has three copies, and tetraploid has four copies.
- Point mutation: A change in a DNA sequence involving a single base pair.
- Polymorphism: The existence of many different alleles for a single gene.
- Promoter: region of DNA involved in the binding of RNA polymerase and gene transcription. This region is often the sequence of DNA 100 to 500 base pairs immediately before the initiation site.
- Recessive: An allele that is not expressed in the presence of a dominant allele.
- Reporter gene: A gene encoding for a new or foreign protein that can easily be detected. For example, the *luciferase* gene, encoding the light-producing proteins of the firefly, is introduced into cells that do not express this gene.



## Chapter 74 Questions - Genetics.doc

- Restriction enzyme: Recognizing specific short sequences of DNA, these enzymes cut the DNA at a particular location.
- Silent mutation: An alteration in a DNA sequence that does not change the product of the gene.
- Southern blotting: A technique of transferring denatured DNA from an agarose gel to a nitrocellulose filter for hybridization with complementary DNA.
- Splicing: removal of introns (spliced out) and the connection of exons (spliced together) in RNA.
- Transcription: Synthesis of RNA on a DNA template.
- Transfection: The addition of DNA sequences to a cell.
- Transgenic animals: Animals created by introduction of new DNA into germ line (into the egg).
- Translation: Synthesis of protein from the messenger RNA template.
- Vector: A plasmid, bacteriophage, or virus that carries new DNA into a cell. Vectors are often designed to produce large amounts of protein encoded by the gene within the host cell.

### What are the different elements that make up DNA?

- base
  - either pyrimidine or purine
- sugar
  - DNA: 2-deoxyribose
  - RNA: ribose
- phosphate
  - links individual nucleotides together

### Describe the process of DNA transcription.

- RNA polymerase II synthesizes 1<sup>st</sup> copy of DNA into RNA
  - direct replica of template DNA
  - contains introns and exons
- introns are spliced out to make mRNA
- mRNA undergoes modification prior to transport into cytoplasm
  - 5' end: guanine added, leading to formation of methylated cap
  - 3' end: chain of 200 adenines added: called poly-A tail
- RNA can undergo alternative splicing to include or exclude certain exons
  - can create different protein isoforms

### What are the different components involved in transcriptional regulation?

- specific sequences within the DNA
  - DNA provides specific docking sites for proteins that enhance the activity of the transcriptional machinery
  - response elements = other sequences found in promoter or enhancer regions of gene
    - promote the initiation of gene transcription
- proteins that interact w/ those sequences
  - Sp1 recognizes and binds to GGGCGG

### What is the role of the nuclear matrix?

- central role in the regulation of cellular processes
  - is the framework or scaffolding of the nucleus
  - consists of peripheral lamin and pore complexes, internal ribonucleic protein network, and residual nucleoli
- is the site of mRNA transcription
  - transcription factors sequestered on the nuclear matrix
  - protein composition of nuclear matrix is tissue specific

### Describe the process of mRNA translation.

- initiation: rate limiting step of translation
  - 30S ribosome binds to mRNA and forms an initiation complex that binds a tRNA w/ amino acid attached
    - tRNA (transfer RNA) is a small molecule linked to amino acid at one end and anticodon on other
  - initiation codon is always AUG (methionine)
- elongation: most rapid
  - amino acids added to peptide chain 1 at a time
  - many amino acids encoded by more than 1 codon
  - multiple ribosomes move simultaneously along chain, making new polypeptide chains
- termination
  - signaled by one of the 3 stop codons: UAA, UAG, UGA

## Chapter 74 Questions - Genetics.doc

### What is ubiquitination?

- certain proteins have a defined time and place in cellular function (cell cycle proteins), some may not have correct shape
- small protein ubiquitin linked to protein: tags it for destruction

### What is an oncogene?

- mutated form of normal gene (proto-oncogene)
  - often associated w/ cell proliferation
  - MYC: proto-oncogene that encodes an early-response gene product that regulates cell proliferation
    - c-myc (cellular oncogene) overexpressed in many cancer
  - c-met: codes for hepatocyte growth factor: found in many RCC

### What ways can a proto-oncogene be converted into an oncogene?

- mutation within the coding sequence
  - produces a permanently activated gene
  - cell gets a continuous signal to proliferate, leading to uncontrolled growth
- gene amplification
  - become amplified through errors in chromosomal replication
  - more DNA templates produce many mRNA transcripts w/ overproduction of protein
- chromosomal rearrangement
  - ex: Philadelphia chromosome

### What is a tumour suppressor gene?

- gene that normally acts to restrain or regulate cell growth
- both copies of a tumour suppressor gene need to be inactivated to permit carcinogenesis
  - ex: Rb gene

### What is meant by epigenetic change?

- DNA sequence integrity is preserved but gene expression is altered
  - hypermethylation of DNA
    - occurs only on cytosine nucleotides in the dinucleotide sequence CG
    - expressed in areas known as CpG islands
    - methylation of CpG nucleotides associated w/ decreased transcriptional activity
    - may result in the inactivation of a tumour suppressor gene
      - ◆ occurs in 5' CG island of the glutathione pi-class S-transferase gene

### What are the steps of the cell cycle?

- G<sub>1</sub> (gap 1): cell prepares to duplicate its DNA
  - G<sub>1</sub>S: main checkpoint of control
- S: cell duplicates its DNA
- G<sub>2</sub> (gap 2): cell prepares to divide
  - G<sub>2</sub>M: main checkpoint of control
- M (mitosis phase): cell divides
- G<sub>0</sub>: cell is quiescent

### What proteins regulate the G<sub>1</sub>S checkpoint in the cell cycle?

- p53
  - binds to the promoter region of p53-responsive genes
  - stimulates the transcription of genes responsible for cell cycle arrest, repair of DNA damage, and apoptosis
    - activates DNA repair enzymes if repairable
    - induces apoptosis if cell cannot arrest growth or repair DNA
- cyclin and cyclin dependent kinases (cdk)
  - passage through cell cycle requires sequential activation of cyclins
    - G<sub>1</sub>: cyclins D and E
    - G<sub>1</sub> and S: cyclin A
    - G<sub>2</sub> and M: cyclin B
  - each cyclin paired w/ cdk
    - function at the G<sub>1</sub>S checkpoint to phosphorylate Rb
  - cyclin D expression critical at the G<sub>1</sub>S checkpoint
    - occurs only in response to extracellular signal
- cdk inhibitors

## Chapter 74 Questions - Genetics.doc

- INK4 family of cdk inhibitors directly inhibits the assembly of cyclin D w/ cdk4 and cdk6
  - blocks formation of the cyclin D-cdk4/cdk6 complex
- cip/kip family of cdk inhibitors
  - may facilitate cyclin D-cdk assembly: rarely mutated
- retinoblastoma protein
  - cyclin-cdk complexes phosphorylate Rb (or its family members p107 and p130)
  - induces cell division: loss of Rb function leads to uncontrolled cell division

### What stimuli may alter p53 expression?

- radiation
  - stimulates the activity of ataxia telangiectasia mutated (ATM) kinase
  - increases p53 activity by phosphorylation
- hypoxia
- oxidation-reduction reactions
- oncogenes

### What is the most commonly mutated human gene in human tumours, including GU malignancies?

- p53
  - 50% of all tumours have p53 malignancies
  - frequent in TCC: associated w/ high-grade muscle invasive disease
    - predicts risk of recurrence, response to chemo

### What stimuli regulate the G<sub>2</sub>M checkpoint in the cell cycle?

- responds only to DNA damage
  - important point for replication errors
  - DNA damage from rads induces G<sub>2</sub>M arrest from protein kinase chk1
  - may also be regulated by p53

### What cellular systems exist to repair DNA damage?

- Nucleotide excision repair (NER)
  - major defense against DNA damage from UV radiation and chemical exposure
  - recognizes distortions in the DNA helix, excising the damaged DNA, and replacing it w/ correct sequence
- Base excision repair (BER)
  - repairs damage from variety of events:
    - spontaneous deamination of bases
    - rads
    - oxidative stress
    - alkylating agents
    - replication errors
  - critical for repairs of oxidative lesions caused by reactive oxygen species (ROS)
  - initial step: removal of a base, rather than a nucleotide
  - no inherited conditions from BER defects
- Mismatch repair (MMR)
  - functions to reverse errors from DNA polymerase
  - proteins responsible: MSH2, MLH1, PMS1, PMS2, MSH6
  - MSH2/MSH3 mediates repair of insertion and deletion
  - MSH2/MSH6 recognizes single nucleotide mismatches in addition
- Double-stranded break repair (DSBR)
  - 2 methods: homologous recombination or nonhomologous DNA repair
  - Ku protein: heterodimer that initiates DSBR by binding to broken end of DNA
    - combines w/ DNA-dependent protein kinase (DNA-PK) and activates kinase activity
      - ◆ phosphorylates many proteins, including Ku
    - phosphorylated Ku is a helicase that unwinds damaged DNA and allows DNA polymerase and ligase to repair the break

### What is the function of apoptosis?

- allows multicellular organisms to eliminate potentially harmful cells
  - protective mechanism against DNA damage
  - role in normal development, tissue homeostasis, and defense against pathogens
  - critical in immune system's ability to eliminate cancer cells

## Chapter 74 Questions - Genetics.doc

### What are the phases of apoptosis?

- trigger of cell death via caspases
  - extracellular signals transmitted to apoptotic machinery via death receptors
    - receptors belong to TNF superfamily: contain ligand-specific extracellular domain + intracellular death domain
  - initiator caspases activate effector caspases
- CD95 death receptor
  - CD95L (ligand) forms a trimer that binds 3 CD95 receptors
  - allows the protein FADD to bind to CD95 via their death domains
  - procaspase 8 → caspase 8

### What is the mechanism by which bcl-2 family members induce cell death?

- by increasing mitochondrial membrane permeability
  - increased in most hormone refractory prostate cancer cells → relative resistance to apoptosis

### What is the role of telomerase in the cell?

- expressed in cells that need to divide an unlimited # of times: gametes, stem cells
- immortalizes cells by maintaining ends of the chromosomes (telomeres) which normally shorten w/ each division
  - DNA polymerase cannot replicate DNA in 3' to 5' direction
  - polymerase replicates other strand discontinuously and ligates the sequences together
  - RNA primers initiate these short strands of DNA
  - telomerase extends the 3' end of the parental strand

### How can TGF- $\beta$ promote tumour progression?

- enhances angiogenesis
- suppresses the immune system
- stimulates the production and turnover of extracellular matrix: provides physical support

### How can one classify cellular receptors?

- Membrane bound (cell surface) receptors
  - Ion channel-linked receptors
    - rapid on /off signal, ideal for conducting nervous impulses to muscle
    - ex: ACh receptor
  - Enzyme-linked receptors
    - Receptor tyrosine kinases
      - ◆ ex: EGF receptor, VEGF, NGF, FGF, IGF-1, PDGF
      - ◆ initiate intracellular signalling by phosphorylating themselves
      - ◆ have an intracellular activating domain covalently linked to the extracellular binding domain
    - Tyrosine kinase-associated receptors
      - ◆ ex: IL-2 receptor
      - ◆ work through associated proteins
    - Receptor serine/threonine kinases
      - ◆ ex: TGF- $\beta$  superfamily of receptors
    - Receptor tyrosine phosphatases
    - Receptor guanylyl cyclases
  - G-protein linked receptors
    - activate intracellular responses through trimeric GTP-binding proteins
- Intracellular receptors
  - Androgen receptor
    - direct interaction of the receptor-ligand complex w/ DNA

### How often are viruses felt to be related to malignancy?

- causally related to 1 in 7 human malignancies

### By what mechanisms do viruses contribute to malignant transformation?

- acutely transforming retroviruses
  - transform all infected cells
- genomic insertion
  - activate a host organism's oncogene or inactivating a tumour suppressor gene

## **Chapter 74 Questions - Genetics.doc**

### **How does EBV induce tumour formation?**

- causes B lymphocyte proliferation in most pts
- translocation of the *c-myc* oncogene

### **What are the mechanisms by which angiogenesis inhibitors act?**

- prevention of tumour cell production of angiogenesis factors
  - IFN- $\alpha$  and IFN- $\beta$  block production of bFGF
- neutralization of angiogenesis factors
  - suramin blocks angiogenic growth factor/receptor interaction
- blocking of the response of endothelial cells to angiogenic factors
  - activity of thrombospondin
- interference w/ matrix degeneration required for vessels to sprout and grow through solid tissues

### **What are the various types of angiogenesis inhibitors?**

- chemotherapeutic drugs
- anticancer treatments
  - ex: hyperthermia
- antibiotics
- proteolytic products of inactive molecules
- endogenous angiogenesis inhibitors
- protease inhibitors
- thalidomide



## Chapter 75

### • Renal Tumours •

#### How can one classify renal tumours?

- Anatomic
  - Tumours of renal capsule: fibroma, leiomyoma, lipoma, mixed
  - Tumours of mature renal parenchyma: adenoma, adenocarcinoma (hypernephroma, RCC, alveolar ca)
  - Tumours of immature renal parenchyma: Wilms', embryonic carcinoma, sarcoma
  - Tumours of renal pelvis: TCC, SCC, adenoca, papilloma
  - Cysts: solitary, unilateral multiple, calyceal, pyogenic, calcified, tubular ectasia, TS, cystadenoma, papillary cystadenoma, dermoid, pararenal/perirenal cysts (hydrocele renalis, lymphatic, Wolffian), malignant
  - Vascular tumours: hemangioma, hamartoma, lymphangioma
  - Neurogenic tumours: neuroblastoma, sympathicoblastoma, schwannoma
  - Heteroplastic tissue tumours: adipose, smooth muscle, adrenal rest, endometriosis, cartilage, bone
  - Mesenchymal derivatives: fibroma, fibrosarcoma, osteogenic sarcoma, lipoma, liposarcoma, leiomyoma, leiomyosarcoma, RMS
  - Pararenal/perirenal solid tumours: lipoma, sarcoma, liposarcoma, fibrosarcoma, lymphangiosarcoma, teratoma, lymphoblastoma, neuroblastoma, Hodgkin's
  - Secondary tumours: sarcoma, blastoma, granuloma, thymoma, testicular, renal
- Simplified anatomic
  - Benign: renal cyst, renal cortical adenoma, metanephric adenoma, oncocytoma, AML, multiloculated cystic nephroma, leiomyoma, renal capsule, parenchyma, vascular, cystic, heteroplastic, oncocytoma
  - Renal pelvis: papilloma, TCC, SCC, adenoca
  - Pararenal: benign, malignant
  - Embryonic: Wilms', embryonic, sarcoma
  - Nephrocarcinoma: RCC, adenoca, papillary cystadenoma
  - Other: primary (MM, mesenchymal, hemangiopericytoma), secondary
- Pathology
  - Malignant: RCC, lymphoma, leiomyosarcoma, RMS, hemangiopericytoma, leiomyosarcoma, Schwannoma, osteosarcoma, fibrous histiocytoma, mets, invx from adjacent ca, carcinoid, Wilms', mesoblastic nephroma, leukemia
  - Benign: simple cyst, AML, oncocytoma, pseudotumour, reninoma, pheo, leiomyoma, hemangioma, cystic nephroma, fibroma, AVM, hemangiopericytoma, RAA
  - Inflammatory: abscess, pyelo, XGP, infected renal cyst, TB, rheumatic granuloma
- Radiologic appearance
  - Simple cyst: cyst, multiple, peripelvic cyst, calyceal diverticulum
  - Complex cyst: cystic nephroma, RCC, hemorrhagic cyst, mets, Wilms', infected cyst, lymphoma, TB, septated cyst, RAA, AVM, hydrocalyx
  - Fatty tumours: AML, lipoma, liposarcoma
  - Others: RCC, mets, lymphoma, sarcoma, lobar nephronia, abscess, TB, oncocytoma, fibroma, XGP, pheo, Wilms', rheumatic granuloma, reninoma, leiomyoma, hemangioma, nephroblastomatosis, adenoca, TCC, carcinoid

#### Why were RCCs originally called hypernephromas?

- 1894: idea of suprarenal origin of renal tumours

#### How can one radiographically evaluate renal masses?

- IVP
  - may miss small anterior or posterior lesions
  - cannot use if ARF
- US
  - will differentiate b/w solid and fluid
- CT abdo
  - for any mass that is not clearly a simple cyst by US

## **Chapter 75 Questions - RCC.doc**

- any enhancing mass is RCC until proven otherwise
- if fat present, is AML
- MRI
  - used w/ pt allergic to contrast, ARF
- renal arteriography

### **What are the features suggestive of malignancy on IVP?**

- calcification w/i the mass
- increased tissue density
- irregular margin
- invasion of the collecting system

### **What are the criteria required for US diagnosis of simple cyst?**

- smooth cyst wall
- round
- no internal echoes
- through transmission w/ posterior enhancement

### **What are the causes of renal pseudotumours?**

- hypertrophied column of Bertin
- renal dysmorphism
- unusually shaped kidney

### **What is the role of FNA in evaluation of renal masses?**

- limited value
  - high incidence of false negative biopsies
- Indications
  - renal abscess or infected cyst suspected
  - RCC must be differentiated from met or lymphoma

### **What is the Bosniak classification of renal cystic masses?**

- Bosniak I: simple, benign cysts
- Bosniak II: minimally complicated cysts
  - septations, minimal calcium, infected cysts, hyperdense cysts (no enhancement, round, sharply marginated)
  - IIF: not well defined by Bosniak → minimally complicated class II lesion that requires follow-up
- Bosniak III: more complicated cysts → operate
  - irregular margin, thick septa, thick calcification
- Bosniak IV: solid component → operate
  - irregular shaggy margins, solid enhancing component

### **What % of small solid CT-enhancing renal masses turn out to be benign?**

- 10-15%: renal adenoma (?), oncocytoma

### **What is a renal (papillary/cortical) adenoma?**

- small, ?benign solid renal cortical lesion
- dx remains controversial – all may be considered to be RCC
- cannot differentiate b/w adenoma and RCC histologically
  - tumour size originally used 3cm cutoff, now changed to 1cm w/ nuclear grade 1 (some say 5mm)

### **What is the treatment for renal adenomas?**

- consider all to be malignant
  - consider wedge resection, other ablative therapies

### **What are the RF for developing renal cortical adenomas?**

- increasing pt age
- VHL
- ARCD associated w/ ESRD
- male
- tobacco use

## Chapter 75 Questions - RCC.doc

### Describe the histologic appearance of a typical renal adenoma.

- small well-circumscribed lesion characterized by uniform basophilic or eosinophilic cells w/ monotonous nuclear and cellular characteristics
- tubulopapillary or purely papillary pattern
- <5mm
- Psammoma bodies

### What is a metanephric adenoma?

- renal mass lesion w/ distinctive histologic features and **benign clinical course**
  - small intensely basophilic cells in acinar pattern, occasional tubular or papillary structures w/ acellular stroma
    - many have scarring or calcification
  - flank pain, gross hematuria, palpable mass
  - polycythemia, hypercalcemia
  - hypovascular tumour
- require excision due to concern about malignancy

### What are the microscopic and gross features of oncocytoma?

- benign mass, 3-7% of all solid renal masses
- Gross: light brown to tan, homogenous, central scar
- Micro: large amount of round or polygonal eosinophilic cells, **numerous large mitochondria → foamy pink**
  - most are low grade: may have prominent nucleoli, pleomorphism, cellular atypia
  - hemorrhage, perirenal fat involvement, microvascular invasion: not as common
  - extension into perinephric fat: doesn't make it malignant
  - occasional oncoblasts

### What are the common cytogenetic findings for oncocytoma?

- loss of chromosomes 1 and Y
- loss of heterozygosity on chromosome 14q
- rearrangements at 11q13

### What is the radiologic appearance of oncocytoma?

- central stellate scar on CT
- spoke-wheel pattern of feeding arteries on angiography
  - **both are unreliable → poor predictive value, cannot be differentiated from RCC**
- increased uptake in oncocytomas on <sup>99m</sup>Tc sestamibi images
- well-defined capsule, central stellate scar, distinctive intensities on T1 and T2 in MRI

### Why is biopsy of limited value in diagnosing oncocytoma?

- difficult to distinguish oncocytoma from granular form of conventional clear cell RCC or eosinophilic variant of chromophobe
- coexistence of RCC and oncocytoma in same lesion

### What is the treatment of oncocytoma?

- treat aggressively w/ exploration and nephron-sparing surgery

### What is an angiomyolipoma?

- benign clonal neoplasm that consists of varying amounts of mature adipose tissue, smooth muscle, and thick-walled vessels
- derived from perivascular epithelioid cells

### Which patient groups are at increased risk of developing AML?

- tuberous sclerosis → 20% of all AMLs
- female predominance

### What is Wunderlich's syndrome?

- massive retroperitoneal hemorrhage from AML
  - increased incidence in pregnancy
- present w/ flank pain, hematuria, mass, and hypovolemic shock

### How can one make a diagnosis of AML?



## **Chapter 75 Questions - RCC.doc**

- CT abdo: small amount of fat excludes RCC
  - only 5 reported cases of RCC w/ fat → all had calcification
  - calcification never reported in an AML
- +ve immunoreactivity for HMB-45 (monoclonal Ab against a melanoma Ag)

### **What is the natural hx of AML?**

- usually asymptomatic if < 4cm
- > 4cm: 82% symptomatic (Oesterling), 9% in hemorrhagic shock at time of presentation
- solitary AML: 5% growth rate / year
- multicentric AML and pts w/ TS: growth rate of 20% per year

### **What is the management of AML?**

- <4cm: follow expectantly w/ repeat imaging q6-12mo
- intervene in larger tumours: partial nephrectomy or selective embolization

### **What is the gross and microscopic appearance of multiloculated cystic nephroma?**

- characteristic renal lesion w/ benign course
- Gross: well circumscribed and encapsulated, multiple noncommunicating fluid-filled spaces partitioned by septa
  - all qualify as Bosniak class III cysts
- Micro: cysts lined by cuboidal epithelium cells arranged in hobnail pattern

### **Describe the epidemiologic distribution of multiloculated cystic nephroma.**

- bimodal age distribution
- male predominance in children → age 2-3
- female predominance in adults → age 30-40: **middle aged women**

### **Describe the presentation of multiloculated cystic nephroma.**

- children: asymptomatic abdominal mass
- adults: abdo pain, UTI, htn

### **How can one distinguish multiloculated cystic nephroma from a cystic RCC?**

- no clinical or radiographic means

### **What is the treatment of multiloculated cystic nephroma?**

- nephrectomy: radical or partial
  - radical more common in kids: concern about Wilms'

### **From which tissue does renal leiomyoma usually arise?**

- renal capsule
- peripelvic tissues
- renal vein

### **What is the presentation of leiomyoma?**

- pain, hematuria, GI complaints if large
- asymptomatic if small

### **What is the tissue origin of a reninoma?**

- derived from the juxtaglomerular cell

### **What is the clinical presentation of reninoma?**

- htn, hypokalemia
- polydipsia, polyuria, myalgia, headaches

### **Describe the epidemiology of RCC.**

- 3% of all adult malignancies
- 30000 new cases each year in US, 12000 pts die each year due to the disease
- slight male predominance → male: female 3:2
- primarily elderly
- 10-20% higher in blacks
- uncommon in children → more likely to be papillary

## **Chapter 75 Questions - RCC.doc**

### **What is the tissue origin of RCC?**

- clear cell: arises from PCT
- chromophobic and papillary RCC: from DCT

### **What are the potential etiologic factors implicated in RCC?**

- viruses
- occupational exposure: lead, petrol, cadmium, asbestos
- htn
- retroperitoneal radiation

### **What are the RF for developing RCC?**

- **smoking → only generally accepted RF**
- obesity
- low socioeconomic status
- urban background
- familial/genetic: VHL, TS
- ESRD: dialysis
- male
- black
- occupational exposure: lead, petrol, cadmium, asbestos

### **What is the familial form of the common clear cell variant of RCC?**

- VHL: AD disorder

### **What are the major manifestations of VHL?**

- retinal angioma
- CNS hemangioblastoma
- RCC
- pheochromocytoma
- renal cysts
- pancreatic adenocarcinoma
- pancreatic cysts
- epididymal cystadenoma
- endolymphatic sac tumour

### **What is the most common cause for mortality in VHL?**

- RCC

### **What is the gene involved in VHL?**

- VHL tumour suppressor gene at 3p25-26

### **What is the VHL gene protein product?**

- mutation of VHL gene leads to dysregulated expression of HIF-1 (hypoxia inducing factor 1)  
→ leads to upregulation of VEGF

### **What genes are potentially involved in the development of RCC?**

- VHL gene
- p53
- tumour suppressor gene at 3p12

### **What is the usual genetic abnormality seen in papillary RCC?**

- trisomy for chromosome 7 and 17
- abnormalities in 1, 6, Y

### **What familial form of RCC exists other than VHL?**

- HPRCC: hereditary papillary RCC  
→ multifocal and bilateral papillary RCC  
→ AD transmission

## Chapter 75 Questions - RCC.doc

### What is the gene mutation in HPRCC?

- missense mutation of MET proto-oncogene at 7q31

### What is the protein product of the MET proto-oncogene?

- receptor tyrosine kinase for the hepatocyte growth factor (aka scatter factor)
  - role in regulation of proliferation and differentiation of epithelial and endothelial cells in many organs

### What tumour-associated antigens are expressed by RCC?

- PRAME
- RAGE-1
- gp75
- MN-9 (carbonic anhydrase 9) → most specific
  - peptides derived from MN-9 can activate cytotoxic T cells

### What observations support impaired immune surveillance in RCC?

- deficient recruitment and activation of dendritic cells
- reduced expression of MHC Ag by tumour cells
- deficient processing of MHC Ag by lymphocytes
- impaired proliferation, locomotion, and cytotoxicity of TILs
- enhanced expression of various immunosuppressive cytokines (IL-10)
- increased expression of the Fas receptor (CD95) by TILs
- impaired activation of NF- $\kappa$ B in TILs and dendritic cells → predisposes lymphocytes to induction of apoptosis and contributes to immune dysfunction

### How does RCC remain resistant to chemotherapeutic agents?

- expression of multidrug resistance (MDR) proteins → MDR-1 (aka P-glycoprotein)
  - acts as energy-dependent efflux pump for many hydrophobic compounds (like chemo)

### What drugs can reverse the MDR-1 phenotype?

- CCB
- calmodulin antagonists
- steroids
- CSA
- tamoxifen
- amiodarone
- quinidine

### How do interactions among cancer cells and adjacent cells in RCC influence its pathogenic potential?

- altered intracellular processing and secretion of fibronectin and other matrix protein in RCC
- increased expression of proteases
- downregulation of C-adherin and cadherin-6 (mediate adhesion b/w cancer cells)

### How can one grade RCC?

- Fuhrman nuclear grade → prognostic significance independent of stage
  - Grade 1: nuclear size 10 $\mu$ m, outline round & uniform, nucleoli absent or inconspicuous (5 yr survival 64%)
  - Grade 2: nuclear size 15 $\mu$ m, irregular outline, small nucleoli (34%)
  - Grade 3: nuclear size 20 $\mu$ m, irregular outline, prominent nucleoli (31%)
  - Grade 4: nuclear size >20 $\mu$ m, bizarre multilobed outline, prominent nucleoli w/ heavy clumps of chromatin (10%)

### What are the histologic subtypes of RCC?

- common/conventional clear cell: 70-80%
  - clear cell, granular cell, or mixed
  - chromosome 3 and VHL mutations are common
  - usually unilateral and unifocal
  - variegated pattern: many colours, cytoplasm full of lipid and glycogen, some hemorrhage (Linda Sugar)
- papillary / tubulopapillary: 10-15%
  - commonly found in pts w/ ESRD and ARCD
  - activations of c-MET proto-oncogene, trisomy of 7 and 17, loss of Y common
  - more likely to be **hypovascular**, due to lack of VHL mutations
  - more likely to be bilateral and **multicentric** (40%)

## Chapter 75 Questions - RCC.doc

- prognosis tends toward well-encapsulated low-grade disease (if Type 1 papillary) → controversial
- basophilic or eosinophilic cells in papillary or tubular pattern, foamy histiocytes (xanthomatous)
- chromophobe: 4-5%
  - loss of Y and 1, monosomy 2,6,10,13,17,21
  - derived from cortical collecting duct
  - EM findings: numerous microvesicles, perinuclear clearing
    - fine reticular pattern: "plant cell appearance"
  - clinical behaviour not known → may actually do better: tendency to remain localized
- collecting duct (Bellini's): <1%
  - younger pts
  - derived from medulla: "plant cell appearance"
  - hard and white: causes reaction in stroma
  - high grade and advanced stage at dx → poor prognosis (2 year life expectancy)
- renal medullary cell
  - almost exclusively in association w/ sickle cell trait in blacks, usually in 20s
  - arise from calyceal epithelium near renal papillae
  - often highly infiltrative, locally advanced and metastatic at dx → poor response and prognosis
- sarcomatoid – no longer considered a distinct variant, but found in association w/ other subtypes (clear cell)
  - aggressive local and metastatic behaviour, poor prognosis → median survival < 1yr
  - automatic Fuhrman grade 4
  - very white, spindle cells (elongated fusiform cells)
  - keratin stain helpful
- unclassified

### Describe the clinical presentation of RCC.

- asymptomatic and nonpalpable until advanced
  - >50% of RCCs now detected incidentally
- sx due to local tumour growth, hemorrhage, paraneoplastic syndromes, or mets
- classic triad: flank pain, gross hematuria, and palpable abdominal mass → rarely found
- indicators of advanced disease
  - constitutional sx: wt loss, fever, NS, bone pain, persistent cough
  - p/e: palpable cervical l/a, nonreducing varicocele, bilateral lower extremity edema
  - skin nodules: rare
  - paraneoplastic syndromes

### What paraneoplastic syndromes are associated w/ RCC?

- increased ESR
- hypertension: due to increased prdx of renin by tumour, compression/encasement of renal artery (RAS), AV fistula in tumour
- anemia
- cachexia and wt loss
- pyrexia
- abnormal LFT (Stauffer's syndrome)
  - increased ALP, PTT, bili, transaminases, decreased albumin
  - must exclude hepatic mets
  - due to increased levels of IL-6
  - hepatic fn normalized after nephrectomy in 60-70%
- hypercalcemia: due to paraneoplastic phenom, or due to osteolytic metastatic involvement
  - production of PTH-like peptides, tumour derived vitamin D and PGs
  - sx: N/V, anorexia, fatigue, lethargy, decreased DTRs
- polycythemia: due to increased prdx of EPO
- neuromyopathy
- amyloidosis
- Cushing's
- hyperglycemia
- galactorrhea
- clotting d/o

### What are the target populations for screening for RCC?

- ESRD

## Chapter 75 Questions - RCC.doc

- RR 5-100X higher than general pplx
- 15% of pts w/ RCC and ESRD have mets
- screen only pts w/ long life expectancy and no medical comorbidities
- CT/US beginning 3<sup>rd</sup> yr on IHD
- VHL pts and relatives
  - yearly PHE and ophtho exam, urinary catechols q1-2yrs
  - q6mo MRI of CNS
  - US abdo/pelvis qyear at age 11, CT q6mo if masses develop
  - periodic ear exams
  - relatives: genetic analysis
- other familial forms of RCC
  - periodic US or CT, consider genetic analysis
- TS
  - periodic screening w/ US or CT → can follow AMLs as well
- **ADPKD → not justified**

### Describe the Robson staging of RCC.

- Stage I: tumour within renal capsule
- Stage II: tumour invasion of perinephric fat (confined to Gerota's)
- Stage III: tumour involvement of regional LN and/or renal vein and IVC
- Stage IV: adjacent organs or distant mets

### Describe the TNM staging of RCC

- 1997 AJCC staging
  - T: primary tumour
    - TX: primary tumour cannot be assessed
    - T0: no evidence of primary
    - T1: tumour 7cm or less, confined to renal parenchyma (previously 2.5cm, changed since not prognostic)
      - ◆ T1a: 4cm or less
      - ◆ T1b: 4-7cm → optional division
    - T2: tumour >7cm in greatest diameter, confined to kidney
    - T3: tumour extends into mj veins or invades adrenal or perinephric tissues but not beyond Gerota's
      - ◆ T3a: invades adrenal directly or perinephric tissues (renal sinus fat)
      - ◆ T3b: grossly extends into renal vein or IVC below diaphragm
      - ◆ T3c: IVC above diaphragm
    - T4: tumour extends beyond Gerota's
  - N: regional LN
    - NX: cannot be assessed
    - N0: no regional LN mets
    - N1: single regional LN met
    - N2: multiple regional LN mets
  - M: distant mets
    - MX: cannot assess distant mets
    - M0: no distant mets
    - M1: distant mets

### Describe the stage grouping for RCC.

- Stage I: **T1N0M0**
- Stage II: **T2N0M0**
- Stage III: **T1-2N1M0, T3N0-1M0**
- Stage IV: **T4, N2, or M1**

### How does one stage RCC?

- Hx
  - sx: bone pain, wt loss, poor performance status = advanced disease
- P/E
  - palpable mass, l/a, nonreducing varicocele, lower extremity edema
- Labs
  - LFT, CBC
- Imaging

## Chapter 75 Questions - RCC.doc

- CT abdo: sensitivity for detection of renal tumour thrombus or IVC involvement 78% and 96%
- CXR
- MRI: gold standard for evaluation of tumour thrombus
- *bone scan: only if increased ALP or bone pain*
- *CT chest: only if abnormal CXR or chest sx*
- **more thorough imaging if locally advanced disease, enlarged retroperitoneal LN, or significant comorbid disease**
- Tissue diagnosis
  - FNAB

### What are the indications for MRI in RCC?

- locally advanced malignancy
- possible venous involvement
- renal insufficiency
- allergy to IV contrast

### What CT findings suggest invasion into perinephric fat?

- perinephric stranding
- distinct soft tissue density within the perinephric space

### What findings suggest ipsilateral adrenal invasion?

- CT
  - enlarged adrenal gland
  - upper pole tumour location
  - extensive malignant replacement of the kidney
- palpably abnormal adrenal gland

### What CT findings suggest venous involvement of RCC?

- venous enlargement
- abrupt change in caliber of vessel
- intraluminal areas of decreased density or filling defects
- collateral vessels

### What are the indications for FNAB/core biopsy of renal mass?

- suspicion of renal abscess
- r/o lymphoma
- r/o mets (hx non-renal malignancy)

### What are the complications of FNAB?

- bleeding
- infection
- AV fistula
- needle tract seeding: **only 5 reported cases**
- pneumothorax

### What are the most important prognostic factors for RCC?

- **pathologic stage → single most important factor**
  - tumour size
- nuclear grade
- histologic subtype

### What clinical findings suggest a poor prognosis in RCC?

- symptomatic presentation
- wt loss > 10%
- poor performance status
- paraneoplastic syndromes: anemia, hypercalcemia, increased ESR

### What are the survival rates like in RCC?

- 5 yr survival 70-90% for T1-2
  - 15-20% reduction in survival associated w/ invasion into perinephric fat

## Chapter 75 Questions - RCC.doc

- 45-70% for venous thrombi if tumour otherwise confined to kidney
  - direct invasion of IVC wall more important prognostic factor than cephalad extent of tumour thrombus
- 5-30% for 5yr and 0-5% for 10yr for LN involvement and systemic mets
  - extended LN dissection may improve survival in this setting

### How does one treat localized RCC?

- radical nephrectomy
- nephron-sparing surgery
- nonextirpative techniques
  - cryosurgery
  - EM energy: laser induced thermotherapy, microwave thermotherapy, RFA thermotherapy
  - mechanical: HIFU (high-intensity focused ultrasound)
- lap vs. open

### What are the basic principles of radical nephrectomy for RCC?

- early ligation of renal vessels
- removal of kidney outside Gerota's
- removal of ipsilateral adrenal gland
- complete regional LND from crus to bifurcation of aorta → controversial

### What are the arguments against regional LND for RCC?

- most pts w/ LN mets have bloodborne mets eventually
- lymphatic drainage of kidney is variable, cannot remove all +ve LN
- many pts w/o mets to regional LN have distant mets

### What are the indications for lap radical nephrectomy for RCC?

- < 8cm lesion
- localized RCC w/ no local invasion
- no renal vein involvement
- no regional l/a

### What are the determinants of distant recurrence after radical nephrectomy?

- stage dependent
  - T1N0M0: 7% distant mets
  - T2N0M0: 26.5%
  - T3N0M0: 40%
- decreasing time to recurrence w/ increasing stage
  - T1: 35mo
  - T2: 25mo
  - T3a: 14mo
  - T3b: 8mo

### What is the postoperative surveillance after radical nephrectomy for localized RCC?

- stage dependent
  - T1: yearly hx/px/blood tests (Ca, ALP, LFT, BUN, Cr, lytes)
    - **yearly imaging not required due to low risk of recurrent malignancy → who doesn't get it, though?**
  - T2: yearly hx/px/blood tests, yearly CXR, CT q2yr
  - T3: q6mo hx/px/blood tests x 3 yrs, then yearly, CXR q6mo x 3 yrs, then yearly, CT at 1 year then q2yr

### What are the accepted indications for nephron-sparing surgery?

- radical nephrectomy would render pt anephric
  - bilateral RCC
  - solitary functioning kidney
- unilateral RCC and functioning opposite kidney affected by a condition that may threaten its future function
  - RAS
  - hydronephrosis
  - chronic pyelo
  - VUR
  - renal calculi
  - systemic diseases: DM, nephrocalcinosis

## Chapter 75 Questions - RCC.doc

- single small (<4cm) RCC and normal contralateral kidney  
→ affected by location of tumour: central vs. peripheral

### What is the need for temporary or permanent dialysis after partial nephrectomy in solitary kidney?

- 8% need IHD temporarily, 4% require permanent IHD (Campbell/Novick, J Urol 1994)  
→ RF for ARF: solitary kidney, tumour > 7cm, >50% parenchymatous excision, >60min ischemic time, ex vivo surgery

### What is included in the evaluation for pts w/ RCC for nephron-sparing surgery?

- CT scan
- renal angio or CT angio

### Which patients are at risk for hyperfiltration injury after nephron-sparing surgery?

- pts w/ > 50% reduction in overall renal mass  
→ proteinuria, FSGS, progressive renal failure  
→ get 24h urinary protein yearly in pts w/ solitary remnant kidney

### What are the possible ways to prevent hyperfiltration injury?

- dietary restriction of protein
- ACEi

### What are the surgical options for pts w/ bilateral RCC and VHL?

- bilateral nephrectomy and renal replacement
- bilateral partial nephrectomy  
→ most eventually develop locally recurrent RCC and need more surgery

### What are the prerequisites for successful cryosurgery?

- rapid freezing
- gradual thawing
- repetition of freeze-thaw cycle  
→ ice-ball should extend 1cm beyond edge of tumour

### What is the mechanism underlying tissue cryodestruction?

- immediate cellular damage  
→ ice formation in ECF → ECF hyperosmotic, causing cellular dehydration and dessication injury  
→ ice formation in ICF → disrupts cellular organelles and cell membrane, and cell dies
- delayed microcirculatory failure  
→ vasoconstriction, endothelial layer destruction, interstitial edema, platelet aggregation, microthrombi, and vascular congestion

### What pts are candidates for observation for RCC?

- small, solid, enhancing, well-marginated, homogenous renal lesions < 3-4cm  
→ possible to have period of initial observation of selected pts
- elderly or poor surgical risk

### What is the natural hx of small renal masses?

- unknown: most removed soon after dx  
→ virtually all pts w/ nephrectomy survive, and have no further cancer related events
- many small renal masses detected in elderly pts w/ comorbidities and increased surgical risk
- retrospective studies suggest that renal tumours < 3cm in diameter rarely metastasize and have a slow growth rate (Bosniak 1995)
- no pts w/ small renal mass < 4cm progress to metastasis that don't already have mets at time of dx (Jewett: Cancer 2004)  
→ 1/3 will grow if managed conservatively

### What is the histology of the small renal mass?

- 40% of renal masses < 2cm are benign (25% 2-4cm)
- 46% benign if 1cm
- most small RCC are low grade
- size of tumour is most important predictor



## **Chapter 75 Questions - RCC.doc**

### **Which pts should not be observed for RCC?**

- lesion > 3cm, or poorly marginated or nonhomogenous lesion
- younger, otherwise healthy individuals

### **What are the signs of IVC involvement of RCC?**

- lower extremity edema
- nonreducing varicocele
- dilated superficial abdominal veins
- proteinuria
- PE
- R atrial mass
- nonfunction of involved kidney

### **What is the significance of arterialization of renal tumour thrombus?**

- pre-op embolization of kidney often causes shrinkage of the thrombus → easier to remove

### **What are the indications for contrast venous venacavography?**

- MRI findings equivocal
- MRI contraindicated

### **What is the usual presentation of pts w/ locally invasive RCC?**

- pain
  - invasion of posterior abdominal wall, nerve roots, or paraspinal muscles
- rare: duodenal or pancreatic invasion → poor prognosis

### **What is the treatment of locally invasive RCC?**

- extended surgical removal
  - en bloc excision of tumour, bowel, spleen, abdominal wall

### **How does one treat local recurrence after radical nephrectomy or partial nephrectomy?**

- surgical excision
  - invasion of local tissue is uncommon
  - local recurrence in 1-10% of pts after nephron-sparing surgery

### **What are the indications for nephrectomy in the setting of metastatic RCC?**

- severe hemorrhage
- severe pain
- paraneoplastic syndromes
- compression of adjacent viscera
- solitary met: improved prognosis if met in lung, adrenal, or brain
  - primary should be the bulk of the disease
- entry into trial

### **What are the advantages and disadvantages of nephrectomy in metastatic RCC?**

- Advantages
  - decreases tumour burden
  - rare response in primary
  - may improve response to immunotherapy: ? induce resolution of mets
  - decreases inhibitors of immune response
  - may impact survival (improvement of survival from 8 to 11 mo: NEJM)
  - palliation (as above)
- Disadvantages
  - response to biologic therapy is low
  - potential morbidity of nephrectomy and biologic therapy
  - will delay immunotherapy
  - may prevent initiation of immunotherapy
  - unnecessary in some pts
  - pts w/ poor performance status not good candidates for OR
  - increased mortality

## **Chapter 75 Questions - RCC.doc**

### **What is the incidence of metastatic disease in RCC?**

- 1/3 of pts w/ RCC have mets at initial presentation
- 40% of the rest develop distant mets

### **What is the role of LND in pts w/ LN+ RCC?**

- low risk pts at low risk of LN mets can be spared LND
- high risk pts (high stage, large size) can be identified
- presence of LN mets poor prognostic factor
- may improve outcomes (decrease regional and distant relapse)

### **What hormonal therapies have been used for treating metastatic RCC?**

- DES
- medroxyprogesterone acetate
- androgens
- antiestrogens
- none of these work

### **What are the results of rads for metastatic RCC?**

- no improvement in survival or local recurrence
- may benefit in treatment of symptomatic bony mets, cord compression, palliation of brain mets

### **Where does RCC metastasize?**

- lung: 50%
- liver: 33%
- bone: 32%
- brain: 25%

### **What are the determinants of a favourable response to immunotherapy for metastatic RCC?**

- good performance status
- previous nephrectomy
- nonbulky pulmonary or soft-tissue mets
- asymptomatic or minimal sx

### **What are the results of immunobiologic therapy for metastatic RCC?**

- IFN
  - 350 pts, Megace vs. IFN: improvement in survival 43% vs. 31% (MRC study, Lancet 1999)
  - 1306 pts, overall RR to IFN- $\alpha$  13.7% (Oncology 1999)
  - 160 pts, vinblastine vs. vinblastine + IFN- $\alpha$ : 2.5% vs. 26%
  - Canadian Urologic Group: 180 pts, IFN- $\gamma$  → no response (overall RR and survival trended to improve in **placebo**)
- IL-2
  - 1714 pts, overall RR 15.4%
  - improved RR if IFN and IL-2 combined
- 5-FU
  - RR 20-40% for IFN, IL-2, and 5-FU

### **How can one administer IL-2 therapy?**

- high-dose bolus
- low-dose bolus
- continuous infusion
- SC injection

### **What are the complications of IL-2 therapy?**

- fluid retention
- interstitial edema
- hypotension
- decreased PVR
- increased CI
- tachycardia
- oliguria
- renal toxicity, azotemia

## Chapter 75 Questions - RCC.doc

### What is meant by adoptive immunotherapy?

- transfer of active immunologic elements w/ anti-tumour reactivity
  - LAK (lymphokine-activated killer) T cells
  - TILs isolated from the tumour itself
  - autologous vaccines to generate sensitized T cells in vivo
- phase 3 trials: no benefit w/ TIL + IL-2 vs. IL-2 alone
  - many of centers that attempted to give TIL could not grow them
  - benefit w/ TIL, but not w/ intention-to-treat analysis

### What are the reasons for nephrectomy prior to immunotherapy?

- surgically decrease tumour burden and enhance response to immunotherapy
- removing the immunosuppressive effects of the tumour
- permitting normal T cell function

### What are the approaches for combining surgery and immunotherapy in pts w/ metastatic RCC?

- initial nephrectomy followed by immunotherapy
- initial immunotherapy then nephrectomy for responders
  - avoids morbidity of nephrectomy in pts that never receive immunotherapy or who don't respond
  - used in pts w/ metastatic RCC w/ solitary kidney
- nephrectomy and immunotherapy followed by resection of residual or recurrent mets
  - survival prolonged in pts w/ resection of mets or residual masses

### What are the signs/sx of renal sarcoma?

- pain, mass, hematuria

### What findings are suggestive of sarcoma rather than RCC?

- origin from capsule
- large size w/o l/a
- fat or bone suggestive of liposarcoma/osteosarcoma
- hypovascular pattern
  - exception: hemangiopericytoma → highly vascular
- very large or rapidly growing mass

### What is the natural hx of renal sarcoma?

- displaces rather than invades parenchyma
  - rapid growth rate
- often metastasize → lungs
- high frequency of recurrence
- prognosis poor, many pts die in months

### What is the treatment for renal sarcoma?

- nephrectomy w/ en bloc resection of adjacent organs
- chemo
  - doxycycline, ifosfamide
- rads + chemo

### What is the most common subtype of renal sarcoma?

- leiomyosarcoma (50-60%)

### What rare form of renal sarcoma can mimic a staghorn stone or XGP?

- osteogenic sarcoma
  - contains calcium → rock hard
  - extensive calcification in a large hypovascular tumour

### How does lymphoma normally occur in the kidney?

- primary lymphoma: rare
- hematogenous dissemination to kidney: most common → 90%
- direct extension from retroperitoneal LN

## **Chapter 75 Questions - RCC.doc**

### **What are the various presentations of renal lymphoma?**

- multiple distinct renal masses
- solitary renal mass
- diffuse renal infiltration
- direct invasion of kidney from enlarged retroperitoneal LN

### **What are the RF for developing renal lymphoma?**

- immune suppression
  - AIDS
  - autoimmune disease
  - GVH disease
- hx of radiation

### **What is the presentation of renal lymphoma?**

- hematuria, flank pain, renal failure
- ureteric obstruction due to enlarged retroperitoneal LN
- hypercalcemia

### **What are the most common sources of mets to the kidney?**

- lung
- breast
- GI
- melanoma
- haem malignancies

### **What is the typical pattern of renal mets?**

- multiple small nodules → clinically silent
  - can cause pain or hematuria

### **How does one dx renal mets?**

- CT or US guided renal bx

### **How does HIFU work?**

- US beams at high power levels and pulse lengths
- energy concentrated in small focal area
- induces coagulative necrosis by heating and cavitation effect
- tissues interposed b/w probe and target not affected





## Chapter 76

### • Urothelial Tumours of the Urinary Tract •

#### How does sex, age, and race affect incidence and mortality of UCC?

- Incidence
  - bladder cancer is 2.5X more common in men: prevalence is 10X the incidence
  - Campbell's states incidence is increasing: may not be true
  - more common as people age
  - 2X more common in white men than blacks: may be non-invasive tumours only
  - 0.5X as common in Hispanics than whites
  - higher incidence in UK and US than Japan and Finland
- Mortality
  - men have higher 5-year survival rates: white men 84%, black men 71%, white women 76%, **black women 51%**
    - **more advanced stage at dx for black**
  - survival by stage at presentation more favourable for whites
  - mortality higher in older people
  - younger ppl have more favourable histology and prognosis: risk for progression same stage-for-stage

#### What factors may lead to a more advanced stage at diagnosis for blacks?

- underreporting of superficial cancers
- delayed diagnosis
- more aggressive variants of UCC in blacks
- less adequate access to or acceptance of therapies
- higher proportion of bladder cancers other than UCC in blacks and females

#### What oncogenes and tumour suppressor genes are associated w/ UCC?

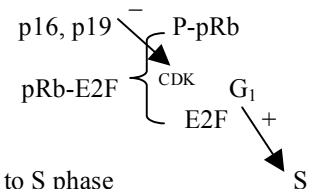
- p21 ras oncogene: GTPase, transducing signals from cell membrane to nucleus
- tumour suppressor genes
  - p53 on chromosome 17p: cause high-grade disease
  - retinoblastoma gene (Rb) on chromosome 13q: cause high-grade disease
  - p19 and p16 on chromosome 9p, 9q: cause low-grade disease

#### What is the function of the p53 gene?

- most frequently altered gene in human cancer
- a transcription factor that suppresses cell proliferation – on 17p
- **directs cells w/ damaged DNA towards apoptosis**
- helps repair damaged DNA by inducing the production of nucleotides
- induces the expression of thrombospondin-1 (TSP-1) → potent inhibitor of angiogenesis

#### What is the function of the Rb gene?

- pRb is normally complexed to E2F
  - phosphorylated by cyclin-dependent kinases, which drives transitions of the cell cycle
  - phosphorylated pRb dissociates from E2F, allowing uncomplexed E2F to induce transit from G1 to S phase



#### What is the function of p16 and p19?

- p16 and p19 inhibit the cyclin-dependent kinases that phosphorylate E2F
- prevent transit from G1 to S phase

#### What are the risk factors for UCC?

- Definite
  - smoking
    - 4X increased risk for UCC: reduction to baseline takes 20 yrs
    - specific carcinogen not known: may increase # of mutations in urothelium
  - analgesic abuse (phenacetin)

## Chapter 76 Questions –Urothelial Tumors

- occupational exposure
  - aniline dyes
  - aromatic amines
  - dietary nitrates and nitrites
- chronic infection
  - *Schistosoma haematobium*
  - HPV: more important in immunocompromised hosts
- long-term indwelling catheter
- bladder stones
- **radiation: high grade and advanced at dx**
- cyclophosphamide: 9X increased risk, most high grade and T2
  - due to acrolein: urinary metabolite of cyclophosphamide
  - short latent period: 6-13 yrs
  - urinary protectant mesna (2-mercaptoethanesulfonic acid) may protect against UCC
- Blackfoot disease (ingestion of arsenic from well water) → endemic in South Taiwan
  - associated w/ vascular and cardiac disease and other numerous cancers
- ingestion of *Aristolochia fangchi* (Chinese herb nephropathy): development of aristolochic acid
- renal transplant recipient: due to immunosuppression
- low amount of fluid ingestion
- Unclear
  - artificial sweeteners: only large volumes in rodents
  - tryptophan metabolites: controversial
  - heredity: few familial clusters → no strong epidemiologic evidence
- Definitely NOT
  - coffee and tea (caffeine)

## What are the RF for recurrence and progression of UCC?

- RF for recurrence
  - **multifocality: #1**
  - grade
  - tumour size
  - incomplete resection
  - stage
  - LOH 9q22.4
  - +ve cysto at 3mo
  - +ve cytology
- RF for progression
  - **pT stage: #1**
  - grade
  - depth of invasion
  - p53 status
  - pRb
  - PCNA
  - ploidy
  - microvessel density (angiogenesis)
- Tumour factors
  - Lymphatic space invasion
  - CIS
  - High grade
  - High stage (invasive)
  - Multifocal and numerous tumours
  - Tumor bulk >4cm or >10g
  - Short time between recurrences and multiple recurrences
  - DNA ploidy status
  - Sessile vs. papillary presentation
  - Previous tumour recurrence
- Chromosomal factors:
  - p53 (17p deletion)
  - Deletion of 9

## Chapter 76 Questions –Urothelial Tumors

- Rb (13q deletion) = unclear
- Aneuploidy
- Patient factors
  - Elderly
  - Irritative voiding symptoms
  - Paraneoplastic symptoms (hyperCa, leukemoid rxns)
  - Anemia
  - Lab:
    - Blood group O
    - T antigen positive
    - EGFR expression
    - CEA and hCG expression

### What enzymes are important in carcinogenic detoxification of smoking in UCC?

- N-acetyl transferase (NAT1, NAT2): acetylation of 4-aminobiphenyl
  - slow acetylators more susceptible to bladder cancer
- glutathione S-transferase M1 (GSTM1)
  - if homozygous for lacking this gene, 2X increased risk

### What are Von Brunn's nests?

- islands of benign urothelium in the lamina

### What is cystitis cystica?

- von Brunn's nests in which the central urothelium has undergone eosinophilic liquefaction

### What is cystitis glandularis?

- similar to cystitis cystica, but transitional cells have undergone glandular metaplasia
  - mucin producing cells
- may be a precursor to adenocarcinoma: perhaps if looks like colonic epithelium

### What is an inverted papilloma?

- benign proliferative lesion associated w/ chronic inflammation or BOO
- papillary fronds project into the fibrovascular stroma of the bladder
- rare malignant transformation into UCC
- **coexists often w/ UCC** elsewhere in the bladder

### What is the difference b/w epithelial hyperplasia, metaplasia, atypia, and dysplasia?

- hyperplasia = increase in # of cell layers w/o nuclear or architectural abnormalities
- metaplasia = change from transitional to nontransitional cell type
- atypical hyperplasia = hyperplasia + nuclear abnormalities and partial derangement of umbrella layer
- dysplasia = epithelial changes that are intermediate b/w normal urothelium and carcinoma in situ

### What is a nephrogenic adenoma?

- lesion that resembles primitive renal collecting **tubules**
  - papillary, polypoid, or sessile
  - can see *hobnailing* pattern
- is a metaplastic response to trauma, infection, or radiation, repeated instrumentation
- associated w/ dysuria and frequency
- precursor to mesonephric adenocarcinoma
  - DDX: papillary cystitis, papillary UCC, adenocarcinoma

### What is vesical leukoplakia?

- a response of the normal urothelium to noxious stimuli
- squamous metaplasia w/ marked keratinization, cellular atypia, and dysplasia
- premalignant lesion that may progress to SCC in 20%

### What is a pseudosarcoma?

- aka postoperative spindle cell nodule, inflammatory pseudotumour
  - rare lesion, looks like leiomyosarcoma
  - benign course



## Chapter 76 Questions –Urothelial Tumors

### What are the premalignant lesions for each type of bladder cancer?

- UCC
  - atypical hyperplasia: increase in # of cell layers + nuclear abnormalities
  - dysplasia = epithelial changes that are intermediate b/w normal urothelium and carcinoma
  - inverted papilloma (glandular type)
  - CIS
- SCC
  - vesical leukoplakia: progresses in 20%
  - squamous metaplasia w/ atypia
- adenocarcinoma
  - cystitis glandularis
  - nephrogenic adenoma: rarely degenerates to mesonephric adenocarcinoma

### What is the relationship of CIS to UCC?

- CIS is present in 25% of pts w/ high-grade superficial UCC (T1G3)
- CIS is present in 20-75% of pts w/ muscle-invasive UCC → direct relationship, is a precursor lesion to invasive bladder ca
- cytology +ve in 80-90% ppl w/ CIS

### How does one grade UCC?

- Features of grading
  - degree of differentiation: how much does it look like normal tissue
  - order (polarity): orderly or disorderly
  - maturation (umbrella cells)
  - nuclear atypia/pleomorphism: most important
  - chromicity
  - mitoses
  - necrosis
- 1998 WHO/ISUP consensus conference: Am J Surg Pathol 22(12): 1435-1448, 1998.
  - grade 0 (papilloma)
    - papillary lesion w/ fine fibrovascular core covered w/ N mucosa
    - does not have > 7 cell layers, nor any abnormalities in histology
    - extremely rare: almost never recurs
  - grade 1 (well-differentiated) = PUNLMP (if confined to mucosa)
    - thin fibrovascular stalk w/ thickened urothelium > 7 cell layers, slight nuclear pleomorphism
    - a.k.a. papillary urothelial tumours of low malignant potential (LMP)
  - grade 2 (moderately-differentiated) = low-grade
    - low-grade urothelial carcinoma
    - wider fibrovascular core, greater disturbance of base-to-surface cellular maturation, loss of cell polarity
  - grade 3 (poorly-differentiated) = high-grade
    - high-grade urothelial carcinoma
    - do not differentiate as they progress, marked nuclear pleomorphism, mitotic figures

### What are the potential etiologies for bladder SCC?

- chronic infection w/ *S. hematobium*: pts 10-20 yrs younger than pts w/ UCC
  - low incidence of LN and distant mets
  - 31% of all cancers in Egypt
- bladder stones
- long-term indwelling catheter
  - paraplegia: SCC in 2-10% w/ indwelling
- chronic UTI
- bladder diverticuli
- smoking
- male

### What is the histology of bladder SCC?

- Gross
  - exophytic, nodular, fungating lesions
- Micro
  - usually well-differentiated

## Chapter 76 Questions –Urothelial Tumors

- low incidence of LN and distant mets
- eccentric aggregates of cells called **squamous/keratin pearls**
- bone is most common site of distant mets
- intercellular cross bridges
- same prognosis stage for stage vs. UCC

### What is the most common site for mets in bladder SCC?

- bone

### How can one classify bladder adenocarcinoma?

- primary vesical
  - usually arise in bladder base or dome
  - most common type in exstrophy
  - most are mucin producing
  - advanced stage at dx: poor prognosis
- urachal: arise outside of the bladder
  - metastasize to iliac and inguinal LN, omentum, liver, lung, bone
  - usually looks like sausage shaped mass arising from dome
- metastatic

### What are the etiologic factors for primary vesical adenocarcinoma?

- bladder **exstrophy**
- **diversion** or augmentation cystoplasty
- schistosomiasis
- chronic UTI
- cystitis glandularis
- nephrogenic adenoma
- urachal cyst or remnant
- mets
  - **always look for colon primary cancer when see adeno of the bladder**

### What are the signs/symptoms of a urachal carcinoma?

- bloody or mucoid discharge from the umbilicus
- mucus in urine if invades into bladder
- mucocele: palpable mass
- **stippled calcifications on Xray**

### What are the most common primary sites of metastatic adenocarcinoma to the bladder?

- rectum, stomach, endometrium, breast, prostate, ovary

### What abnormal biologic processes facilitate invasion in bladder UCC?

- elaboration of angiogenic factors: FGF, VEGF
  - higher expression of EGF receptors
- elaboration of proteases: type IV collagenases (metalloproteinases), urokinase, u-PA
  - degrade fibronectin, cleave plasminogen, laminin
- disruption of intracellular adhesion molecules: E-cadherins, integrins, catenins

### What are the different patterns of bladder cancer spread?

- direct spread
  - en bloc spread (60% - most common): cancer cells invade in broad front directly beneath the primary lesion
  - tentacle-like invasion: in 25%
  - lateral spread: tumour cells grow under normal-appearing mucosa
- metastatic: almost all pts who develop mets develop T2 disease before or at the time mets are recognized
- lymphatic: occur before hematogenous mets
- vascular
  - most common sites of vascular mets: liver (40%), lung (35%), bone (25%), adrenal (20%), gut (15%)
- implantation: usually in high-grade

### What % of men w/ UCC have prostatic involvement?

- 40% of men undergoing cystectomy for T2 disease have prostatic involvement

## Chapter 76 Questions –Urothelial Tumors

- prostatic urethra in most cases
- stromal involvement in 6%

### Describe the natural hx of superficial UCC.

- low grade superficial disease (55%)
  - Ta, T1, Tis: 70%, 20%, 10%
  - majority recur post-resection, 16-25% w/ higher grade lesions
  - 10% develop muscle invasive disease
  - 5% develop vascular or lymphatic spread
- high grade superficial disease (45%)
  - >50% are muscle invasive at the time of diagnosis (84-92% p2755)
  - 20% develop vascular or lymphatic spread

### What % of UCC is T2 at dx?

- 25% muscle invasive
- 75% superficial

### Describe the metastatic spread of UCC.

- most common sites of mets in bladder cancer are pelvic LN
  - obturator 75%, external iliac in 65%, presacral in 25%, paravesical in 15%
- most common sites of vascular spread
  - liver: 40%
  - lung: 35%
  - bone: 25%
  - adrenal: 20%
  - gut: 15%

### What are the most important prognostic parameters in UCC for recurrence and progression?

- grade
- stage
- presence of CIS
- others: lymphatic invasion, tumour size, papillary or solid tumour, multifocality, frequency of prior recurrence, DNA ploidy status, chromosomal factors (deletion of p53, 9, 13q, aneuploidy)

### What lab parameters have been correlated for worse prognosis in UCC?

- lack of A, B, H blood group antigens
- enhanced expression of Lewis<sup>x</sup> blood group antigen
- increased urinary fibronectin
- altered expression of E-cadherin, integrins, catenins
- amplification of c-ERB-b2 oncogene: may be more useful as marker of disease than prognostic indicator

### What is the effect of TGF- $\beta$ on UCC?

- inhibits cellular proliferation
  - stimulate p27 and p15, inhibit pRb
- potent angiogenic activity

### What are the signs/sx of bladder cancer?

- **painless hematuria: most common presenting sx of bladder ca → in 85%**
- LUTS: freq, urge, dysuria → 2<sup>nd</sup> most common
- flank pain from ureteral obstruction
- lower extremity edema
- pelvic mass
- advanced disease: weight loss, abdo/bone pain

### What is the accuracy of urinary cytology?

- more sensitive in pts w/ CIS or high-grade tumours
- 80% sensitivity in pts w/ high-grade tumours (false-negative rate 20%)
- false-positive rate 1-12%
  - due to urothelial atypia, inflammation, rads, chemo
  - may persist for > 1yr after tx

## Chapter 76 Questions –Urothelial Tumors

- barbotage better than voided specimens
  - must indicate to pathology: can get papillary fragments
- features
  - size of cells
  - nuclear:cytoplasm ratio
- cannot differentiate b/w low grade and high grade on cytology

### What diagnostic tests are available to diagnose bladder cancer?

- cytology
- flow cytometry
- quantitative fluorescent image analysis
- marker tests: high sensitivity, but lower specificity → may be best used in follow-up of low risk pts, not in dx
  - expression of A,B,H blood group antigens
  - Lewis<sup>x</sup> blood group
  - antigen M344, T138, EMA
  - excretion of soluble factors in urine: autocrine motility factor and its receptor, basic FGF, EGF, human complement factor H-related protein [BTA (bladder tumour antigen) stat and BTA TRAK → qualitative and quantitative studies respectively]
  - NMP22, HA/HAase
  - ImmunoCyt: cocktail of Ab to M344, another mucin-related Ag, and HMW-CEA detected by immunofluorescent cytology
- imaging
  - excretory urography: indicated in all pts w/ suspected UCC
    - ureteral obstruction = invasive UCC usually
  - retrograde pyelography: if upper tracts not adequately visualized on IVP
  - CT abdo/pelvis: if suspect upper tract tumour
- cystoscopy + bimanual exam
- TURBT
- biopsy
- metastatic workup if appears invasive
  - LFTs
  - CXR: PA and lateral
  - bone scan if ALP elevated

### Which chromosome aberrations are associated w/ low-grade vs. high-grade UCC?

- low-grade papillary superficial tumours: 9q
- high-grade: 7, 9p, 13q, 17p

### How does flow cytometry work?

- requires large cell populations
- measures DNA content of cells whose nuclei are stained w/ DNA-binding fluorescent dye
  - DNA diploid tumours: usually low grade and low stage → favourable prognosis
    - often produce false-negative results
  - triploid to tetraploid chromosome number: unfavourable pathologic characteristics → poor prognosis
- correlation exists b/w proliferative activity (% of tumours in S phase) and tumour progression
- not more useful than cytology

### How does quantitative fluorescent image analysis work?

- automated cytologic technique
- analyzes smears of cells on a microscope slide and measures DNA content in each cell
- can be performed w/ fluorescently labeled DNA probes to specific chromosomes of interest
  - can demonstrate tumours w/ trisomy of chromosome 7, loss of chromosome 9, or 17p deletions

### What are the results of bladder cancer screening studies?

- 20% of pts have hematuria w/ screening
- 6-8% of those undergoing urologic evaluation found to have urothelial cancers
- 1.2-1.3% of all participants found to have bladder cancer
- both screened and unscreened pts had similar proportions of low grade (55%) and high grade (45%) cancers
  - unscreened men: >50% of high grade cancers T2 or greater upon diagnosis
  - screened men: 10% of high-grade screening detected cancers were T2 or greater → screening downstages high-grade ca
    - screening permits dx of bladder ca that would become T2 at earlier stages, allowing decreased mortality
- screening w/ urine dip should be yearly

## Chapter 76 Questions –Urothelial Tumors

- concern re: chemical exposures causing abnormal test results w/o causing malignancy

### What is the utility of the Lewis<sup>x</sup> antigen for bladder ca?

- normally absent from urothelial cells in adults except for occasional umbrella cells
- increased expression in urothelial carcinoma
- immunostaining can detect tumours w/ sensitivity of 86% and specificity of 87%

### What is the utility of random mucosal biopsies at the time of TURBT?

- 20-25% of pts w/ UCC have dysplasia or CIS
- may be predictive of tumour recurrence → some people feel these are not necessary

### What are the indications for random biopsies at TUR?

- partial cystectomy planned
- +ve cytology: if urinary cytology indicates presence of high-grade disease and cysto is –ve or all look superficial
- r/o prostatic involvement

### What are the cons of bladder biopsy in UCC?

- may be unnecessary
- denude epithelium and allow for tumour implantation
- may miss malignancy due to sampling error

### What is the accuracy of staging UCC?

- overstaging in 10%
- understaging in 30%

### What tests are available for staging bladder UCC?

- blood work: LFTs, Ca
- radiologic tests
  - CT: 1<sup>st</sup> test to determine localized vs. locally extensive or metastatic disease
  - MRI: not more helpful than CT for local staging, may be better for bone mets
  - US: minimal value
  - CXR
  - chest CT
  - bone scan: rarely show mets in pts w/ normal LFTs, esp if ALP normal
- lymphadenectomy
  - FNA may be used to document mets
- not needed if tumour is superficial: extremely rare

### What is the utility of 5-ALA?

- 5-aminolevulinic acid administered intravesically w/ cysto using blue light (375-440 nM) can detect lesions invisible w/ white light → increased sensitivity from 77% to 98%

### Why does variation often occur in judging depth of penetration of UCC?

- muscularis mucosa in lamina propria can be confused w/ detrusor
- adipose has also been found in lamina

### How does depth of invasion affect prognosis and survival?

- deep lamina involvement probably confers worse outlook than superficial lamina invasion
- in pts w/o muscularis mucosa in specimen, extent of invasion below urothelial surface (above or below 1.5mm) correlates well w/ progression-free survival
- tumours invading >4mm on TURBT specimen have higher likelihood of having T3 disease → value unknown

### What is the clinical utility of CT scan for staging UCC?

- provides information about presence of pelvic and para-aortic l/a and visceral mets
  - limited accuracy: can detect only gross extravesical extension, LN that are large, and liver mets > 2cm
- CT scan should be done before TURBT
- fail to detect LN mets in 40-70%

### What is the most accurate means of determining regional LN involvement?

- pelvic lymphadenectomy

## Chapter 76 Questions –Urothelial Tumors

### What are the primary regions of lymphatic drainage of the bladder?

- perivesical, hypogastric, obturator, external iliac, presacral LN

### What are the boundaries of dissection in the standard staging lymphadenectomy for bladder cancer?

- remove all nodes from iliac bifurcations to femoral canals
- from genitofemoral nerves to bladder pedicles

### Why are routine CXRs rather than CTs used to rule out pulmonary mets in bladder cancer pts?

- CT scans frequently detect small noncalcified pulmonary lesions → most are granulomas
- most noncalcified lesions >1 cm are mets
- standard films do not have resolution to detect small granulomas

### What is the recommended metastatic evaluation for invasive bladder cancer?

- LFTs
- CXR
- IVP
- abdo/pelvic CT
- bone scan if needed: rarely +ve if normal LFTs (ALP) and no bony sx

### What is the staging system for bladder UCC?

- 1997 UICC AJCC
  - T stage
    - Ta: no invasion into lamina
    - Tis: CIS
    - T1: invasion into lamina
      - ◆ papillary core vs. true lamina: no significance
      - ◆ invasion into muscularis mucosa or arterioles: may be significant → controversial
    - T2: muscle invasive → cannot substage at TURBT (unreliable)
      - ◆ T2a: superficial
      - ◆ T2b: deep
    - T3: extravesical extension
      - ◆ T3a: microscopic
      - ◆ T3b: macroscopic
    - T4: invasion into pelvic viscera
      - ◆ T4a: prostatic stroma, rectum, uterus, vagina
      - ◆ T4b: abdominal wall, pelvic sidewall
  - N stage
    - N1: single node < 2cm
    - N2: multiple nodes < 5cm or single node 2-5cm
    - N3: node >5 cm
  - M stage
    - M0: no distant mets
    - M1: distant mets

### What therapies have been used in the prevention of bladder cancer?

- vitamins: no evidence
  - vitamin A, B<sub>6</sub>, C, Zn, Se
- polyamine synthesis inhibitors
  - DFMO (difluoromethylornithine)
    - induction of ornithine decarboxylase (ODC) is an integral part of tumour promotion
    - DFMO inhibits ODC, prevents experimentally induced tumours
    - major toxicity: ototoxic → uncommon and reversible
- diet
  - urinary acidification: protective against saccharine-induced bladder ca in rats
  - soy products
    - inhibit cyclin dependent kinase-2 activity, induce G2-M cell cycle arrest
  - fluids: dilution of carcinogenic agents → RR 0.51 for highest quartile of fluid ingestion compared w/ lowest
- NSAIDs: interfere w/ variety of cellular processes, may prevent chemically induced UCC
  - COX2 is upregulated in UCC

## Chapter 76 Questions –Urothelial Tumors

- avoidance strategies: stop smoking

### What nonurothelial tumours may involve the bladder?

- small cell carcinoma
  - derived from neuroendocrine stem cells or dendritic cells
  - exhibit neuroendocrine markers: neuron-specific enolase (NSE)
  - aggressive tumours w/ early vascular and muscle invasion
  - evaluate pts for SCLC
  - treat pts systemically, not w/ exent: Jewett, 2004
- carcinosarcoma
  - rare, highly malignant, poor prognosis despite tx
  - contain malignant mesenchymal and epithelial elements: usually osteo/chondrosarcoma + UCC/SCC/adenocarcinoma
  - present w/ gross painless hematuria
- mets
  - most common mets to bladder: prostate, ovary, uterus, lung, breast, kidney, stomach → like any adeno
  - others: melanoma, lymphoma, leukemia
- nonepithelial bladder tumours
  - neurofibroma
    - benign tumour of the nerve sheath resulting from overgrowth of Schwann cells
    - multiple neurofibromas from neurofibromatosis
    - rare malignant transformation to neurofibrosarcoma
  - pheochromocytoma: < 1% of all bladder cancers, <1% of all pheos → 10% are malignant
    - arise from paraganglionic cells within the bladder wall, usually in the region of the trigone
    - often cause paroxysms of htn/syncope on filling or emptying, hematuria in 2/3
    - do not do TURBT: may precipitate hypertensive crisis
    - treat w/ partial cystectomy
  - primary lymphoma: arise from submucosal lymphoid follicles
    - age 40-60, usually F
    - manage as w/ other lymphoma
  - plasmacytoma, melanoma, yolk sac tumour
  - sarcomas: angiosarcoma, hemangioma, leiomyosarcoma, rhabdomyosarcoma
    - leiomyosarcoma is most common malignant mesenchymal tumour that arises in adult bladder
      - ◆ smooth muscle differentiation
    - all generally respond poorly to rads/chemo

### What % of renal tumours are UCCs?

- 10%

### What % of urothelial tumours involve the upper tracts?

- 5%: ureteral tumours only 1%

### How does sex and race affect incidence and mortality of upper tract UCCs?

- ureteral tumours are 2X as common in M vs. F
- 2X as common in whites vs. blacks
- women who develop ureteral cancer have a 25% higher chance of dying vs. men

### What is the association of UCC w/ Balkan nephropathy?

- Balkan endemic nephropathy (BEN) characterized by degenerative interstitial nephropathy
- confined to rural areas of Balkan countries
- tumours low grade, multiple and bilateral
- theories
  - ochratoxin A: pigs exposed to ochratoxin A develop BEN
    - mycotoxin in high concentration in food in the Balkans → #1 theory
  - viral: coronavirus → unlikely
  - defective embryogenesis → unlikely

### What factors have been implicated in the development of upper tract cancers?

- presence of bladder UCC
- age
- sex

## Chapter 76 Questions –Urothelial Tumors

- race
- smoking: 3X increased risk of upper tract UCC → 2X increased risk even if quit
- coffee consumption: strong association w/ smoking, though
- analgesic abuse: phenacetin (222's) → now off the market
  - renal papillary necrosis and phenacetin are synergistic RFs
  - degree of papillary scarring correlates w/ tumour grade
- occupational exposure: chemical, petrochemical, and plastics industries
  - exposure to coal, coke, asphalt, tar
- chronic irritation: causes SCC
  - infection
  - stones
  - schistosomiasis
- hydronephrosis: associated w/ adenocarcinoma
- cyclophosphamide
  - tumours induced by this agent are generally high grade and very aggressive
- Chinese herb nephropathy
  - weight loss herbs contaminated w/ *A. fangchi*: causes UCC by DNA adducts formed by aristolochic acid
  - mean exposure only 2 years, w/ 20% of upper tract UCC already invasive
- heredity
  - Lynch syndrome II: early onset of proximal colonic tumours and extracolonic neoplasms
- htn: ?chronically inflames kidney, ?drugs, confounded by smoking

### What histologic finding is pathognomonic for analgesic abuse?

- thickening of basement membranes around subepithelial capillaries: **capillarosclerosis**

### What % of upper tract tumours are bilateral?

- 2-5% synchronous or metachronous

### What % of pts w/ bladder cancer develop upper tract UCCs?

- 2-4%: mean interval b/w bladder and upper tract UCC 70 months (range 40-170)
  - exception: occupational UCC → 13% upper tract UCC

### What % of pts w/ upper tract tumours develop bladder cancer?

- 25-75%

### What are the indications for repeat upper tract monitoring?

- multiple tumours
- recurrent tumours
- tumours near or involving UO
- CIS

### Where are ureteral tumours usually located?

- usually in lower ureter, least commonly in upper ureter → ?due to seeding from upstream
  - 73% distal ureter
  - 24% mid-ureter
  - 3% proximal ureter

### What are the types of cancers that occur in the ureter?

- UCC: >90%
- SCC: usually associated w/ infected staghorns or analgesic abuse
- adenoca: associated w/ stones, long-term obstruction, and inflammation
- inverted papillomas: 18% incidence of malignancy → should be followed closely
- nonurothelial tumours: sarcomas, small cell, plasmacytomas, fibroepithelial polyps

### What are the different patterns of spread for upper tract UCC?

- direct invasion into renal parenchyma
- epithelial extension: increased upper tract recurrence in bladder ca pts w/ VUR
- lymphatic invasion
- vascular invasion: to liver, lung, bone



## Chapter 76 Questions –Urothelial Tumors

### What are the most common sites for LN spread of upper tract UCCs?

- para-aortic, paracaval, and ipsilateral common iliac and pelvic LNs

### What are the most common sites of hematogenous mets from upper tract UCCs?

- liver, lung, bone

### What is the staging system for upper tract UCCs?

- Ta: epithelially confined papillary lesion
- T1: invades lamina propria
- T2: invasion of muscularis propria
- T3: invasion of peripelvic/periureteral tissue
  - T3 renal pelvis tumours have better prognosis than ureteral → renal parenchyma serves as a barrier
- T4: invasion of contiguous organs
- N1: single LN <2cm
- N2: multiple/single node 2-5cm
- N3: node > 5cm
- M0: no hematogenous or distant mets
- M1: hematogenous or distant mets

### What molecular assays have been used to predict prognosis of upper tract UCCs?

- A,B,H blood group antigen expression
- Thomsen-Freidenreich antigen expression: no correlation
- DNA flow cytometry: more aneuploidy in higher grade lesions
- proliferation markers
  - DNA synthesizing (S phase) fraction
  - MIB-1/Ki67
  - p53 abnormalities
  - MMP-2, MMP-3

### What are the signs/sx of upper tract UCC?

- hematuria: gross or microscopic (75%)
- flank pain/colic (30%)
  - dull: gradual obstruction and distension of collecting system
  - acute colic: passage of blood clots
- pyelo/pyonephrosis
- sx of advanced disease: abdo/flank mass, wt loss, anorexia, bone pain

### How does one diagnose upper tract UCC?

- Imaging
  - IVP: filling defect in 50-75%, obstruction in 10-30%
    - must completely evaluate ureters bilaterally
  - retrograde urography: useful w/ poor or no renal fn
  - anterograde pyelogram: not advised due to seeding → procedure of last resort
  - CT: may show a collecting system tumour better than IVP, but may miss small tumours
  - US abdo: little value in diagnosing upper tract UCC
  - MRI: no advantage over CT
  - best modalities: CT urogram or MR
- cystoscopy: mandatory
- cytology: 40-70% sensitivity
  - voided cytology
  - ureteral catheterization/washings: some have reported good results, others have not
  - brush biopsy
- ureteroscopy and nephroscopy
  - ?necessary: in difficult cases only, not needed in clear cut cases

### What is the radiologic appearance of upper tract SCC?

- infiltrating tumour associated w/ stone or diffuse papillary calcification
  - esp if analgesic abuse suspected

### What is involved in the metastatic workup of upper tract UCC?

## Chapter 76 Questions –Urothelial Tumors

- CT
- CXR
- LFTs
- CrCl
- bone scan if necessary
- renal scan: if compromised renal function

### Why should nonionic contrast be used for retrograde urography?

- hyperosmotic contrast may alter the cellular detail and make cytology more difficult to interpret

### What is the accuracy of cytology in diagnosing upper tract UCC?

- voided urine insensitive in dx of upper tract UCC
  - low-grade tumours: cytology read as normal in 80%
- ureteral catheterization better than voided urine: false-negative in 22-35%, substantial false+ve
  - ureteral washings give better cell yields
- brush biopsy: sensitivity 91%, specificity 88%, accuracy of 89%
  - complications: hemorrhage, UTI, ureteral perf, seeding

### What are the potential disadvantages of performing ureteroscopy in pts w/ upper tract UCC?

- risk of ureteral perforation and extravasation of tumour cells
- denudation of ureteral mucosa, facilitating implantation of tumour
- development of ureteral disruption or stricture formation
- pyelo-venous-lymphatic migration of UCC cells after ureteroscopy
- sampling errors: biopsies not adequate for grading
- not all radiographically visible lesions are accessible to endoscopic inspection
- trivial amounts of hematuria may cloud visibility to make inspection impossible

### What is the clinical utility of endoscopically obtained biopsies to diagnose upper tract UCC?

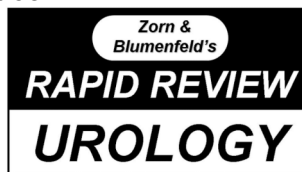
- in 18% of cases, biopsies insufficient size/quality to permit histologic grading
- used only in situations when diagnosis remains in doubt after conventional diagnostic techniques and tx influenced by results of ureteroscopy

### What are the AUA Guidelines for asymptomatic microscopic hematuria?

- definition:  $\geq 3$  RBC/HPF from 2 of 3 properly collected urinalysis specimens
  - if pt is high risk, one sample is enough
    - RF for primary renal disease: significant proteinuria, renal insufficiency, dysmorphic RBC in urine, RBC casts, or increased Cr
    - RF for GU disease: smoker, occ exposure, hx gross hematuria, age  $> 40$ , previous GU d/o, hx LUTS, hx recurrent UTI
- Nephrology evaluation
  - recommend if initial evaluation identifies a pt w/ renal parenchymal disease
  - consider renal bx if systemic causes not identified
- GU evaluation
  - initial evaluation
    - Hx/Px
    - urethral and vaginal examination in women
    - urine specimen: catheter only if vaginal contamination or phimosis
      - ◆ U/A, sediment, RBC/HPF count, presence of dysmorphic RBC or casts, proteinuria
      - ◆ urine C&S
    - serum Cr
  - cytology
    - if RF for UCC
    - as adjunct to cysto if there is a qn of LUTS (esp in determination of CIS)
    - in pt w/o RF for UCC (or perform cystoscopy)
  - imaging: indicated for detection of RCC, UCC, stones, or infection
    - KUB and US: low risk pts w/ contraindication to contrast
    - US and retrograde: higher-risk pts w/ contraindication to contrast
    - MRI: 2<sup>nd</sup> line test
  - cystoscopy
    - recommended in all pts  $> 40$
    - recommend in all pts  $< 40$  w/ RF for bladder cancer

## Chapter 76 Questions –Urothelial Tumors

- ◆ if < 40 and no RF (low risk): cytology only
- Follow up
  - repeat cytology, U/A, and BP at 6, 12, 24, 36 months
  - repeat imaging, cysto or cytology if: gross hematuria, abnormal cytology, or LUTS w/o infection
  - refer to Nephro if hematuria persists + htn, proteinuria, or evidence of glomerular bleeding (casts, dysmorphic RBCs) develop



## **Chapter 77**

### **• Management of Superficial Bladder Cancer •**

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#### **What is the influence of bladder tumour grade and stage on tumour recurrence and progression?**

- low grade Ta lesions: 50-70% recurrence, 5% chance of progression (37% progress overall in grade or stage)
- high grade T1 lesions: >80% recurrence, 50% chance of progression in 3 yrs
  - 10-20% of the total progress to T2 disease

#### **What are the proportions of bladder UCC at presentation by stage?**

- superficial: 70% → 55% low grade, 45% high grade
  - 70% Ta
  - 20% T1 → upstaged in 25% on repeat TUR
  - 10% Tis
- muscle invasive: 30%
  - upper tract: 50-60% renal pelvis tumours are muscle invasive, but 55-75% of ureteral tumours are low grade/stage

#### **What characteristics of a tumour predict behaviour of superficial lesions?**

- grade
- stage
- remaining urothelium (CIS)
- tumour size
- # of lesions
- lymphovascular invasion

#### **What is the use of 5-ALA in cystoscopy?**

- 5-aminolevulinic acid: bladder treated 2-3hrs prior to cysto w/ 3% solution, illuminated w/ 375-445nm light source
- greater sensitivity in detecting urothelial abnormalities (97% vs. 73%)

#### **How should one manage endoscopic resection of lesions in bladder diverticula?**

- resect at the neck of the diverticula and avoid TUR in the deeper portions
  - use cold-cup biopsy and fulgurization

#### **How often is residual tissue seen in repeat TUR?**

- 40-75% of cases → T1 upstaged in 25%

#### **What are the indications for repeat TUR?**

- multifocal disease
- highly recurrent lesions
- high grade disease
- ?muscle invasive disease
- ?all T1 disease

#### **How often is T1 tumour upstaged after repeat resection?**

- 25% demonstrate worse prognosis

#### **What are the complications of TURBT?**

- bladder perforation: extraperitoneal vs. intraperitoneal
  - may result in metastatic spread of superficial lesions
- clot retention
- ureteral orifice scarring

#### **What is the role of random biopsies in TURBT?**

- value of random biopsies of normal-appearing tissue at the time of resection is minimal
  - may aid in tumour implantation

## Chapter 77 Questions - UCC Superficial.doc

- biopsies of suspicious areas are important
- indications: partial cystectomy, +ve cytology w/ normal bladder, r/o prostatic involvement

### What laser is optimal for treatment of UCC?

- Nd:YAG laser at 25W for 3 seconds
  - little bleeding, no obturator reflex
  - CO2 laser: does not operate in a fluid medium → cannot use in bladder
  - found to have fewer recurrences at site of tumour vs. TURBT

### How does photodynamic therapy work for UCC, and how well?

- administer photosensitizing agent: porfimer sodium (Photofrin) at 1.5-2 mg/kg IV
- 2-3 d later, intravesical tx w/ red laser light (630nm) for 12-20 min
  - use intravesical Intralipid for more uniform distribution
- avoid sunlight for 6-8 weeks
- response rate in 66%

### What are the side effects of photodynamic therapy?

- bladder contracture or irritability: 50%
- dermal sensitivity: 19%

### What is the RR for pts that receive BCG for CIS?

- initial response rate of 80%
- pts that fail have 50% progression → should perform cystectomy

### What are the indications for cystectomy in a pt w/ T1 disease?

- CIS refractory to medical therapy
- healthy pt w/ persistent or recurrent high-risk superficial disease that has failed intravesical therapy
- option as initial treatment in high-grade T1 disease, esp. if multifocal → controversial
- failure of BCG = failure to respond to **two 6-week courses of therapy** or **early recurrence of high grade disease**
- low- to moderate-grade polychronotropic superficial disease that renders the bladder nonfunctional
- unresectable low grade disease

### What are the results for cystectomy after superficial disease?

- 70-90% 10 year survival

### Does early cystectomy improve survival in pts w/ superficial disease that recur?

- Yes: Herr 2001 (J Urol)
  - 307 pts w/ high grade superficial disease initially treated w/ BCG and TURBT
  - 90 pts underwent cystectomy for recurrence (35 w/ superficial, 55 w/ progression to T2 disease)
    - 48 vs. 42 pts underwent cystectomy within 2 yrs vs. after 2 yrs: 69% vs. 26% 15 yr survival
      - ◆ superficial (92% vs. 56%), muscle invasive recurrence (41% vs. 18%)
      - ◆ more pts that undergo delayed cystectomy have T2 disease
  - markedly decreased survival in pts that recur w/ T2 disease (83% vs. 27% 15 yr survival)

### What are the alternative therapies for superficial UCC?

- external beam radiation
- chemoprevention
- vitamins
- DFMO: ODC inhibitor of polyamine synthesis
- soy: growth inhibition in vitro
- COX inhibitors
- intravesical chemotherapies

### What is the role for external beam radiotherapy for superficial bladder cancer?

- limited, minimal role
- reserved for pts that refuse cystectomy after failure of intravesical therapy or are unsuitable for cystectomy

### What is the effectiveness of radiation in superficial bladder cancer?

- 5 yr response rates: 44-60%
  - recurrence associated w/ death from disease

## Chapter 77 Questions - UCC Superficial.doc

- 5 yr distant recurrence: 10-25%

### How does water intake affect risk of developing bladder cancer?

- high water intake reduces risk by 50%

### How does intake of vitamins affect risk of developing bladder cancer?

- little evidence for role of single vitamins in prevention
  - no evidence for vitamin E, vitamin A, vitamin B<sub>6</sub>
- megavitamins may decrease recurrence

### What intravesical chemotherapies are available?

- BCG
- mitomycin C
- doxorubicin
- epirubicin
- thiotepa
- valrubicin
- ethoglucid

### What is BCG?

- bacille Calmette-Guerin
  - attenuated mycobacterium used as a vaccine for TB
  - effective in treatment of CIS, residual papillary disease, prophylaxis in recurrent superficial disease

### How does BCG work?

- unknown
  - BCG contacts tumour cells through a novel fibronectin attachment and is internalized
  - upregulation of IL-12, upregulating expression of ICAMs and CD4/CD8 ratio
  - T<sub>H</sub>1 cell response mediates therapeutic effect
  - NOS induction may have a role: high local concentrations of NO inhibit UCC growth

### How does one administer BCG?

- BCG stored as lyophilized powder until instillation at 4°C
- reconstituted in 50cc NS, administered 2-4 weeks post-TURBT, administer under gravity
- retain x 2 hrs

### What are the indications for BCG treatment?

- primary treatment of CIS
- treatment of residual papillary lesion *when resection not possible* → 60% response
  - should not be used as a substitute for TURBT
- CIS of prostatic urethra (after TURBN)
- high grade disease (G3)
- T1 disease, any grade
- multiple, diffuse papillary tumours
- large tumour (>2cm) at initial presentation
- tumour recurrence w/i 1yr of tx
- positive urine cytology after resection of visible tumour
- maintenance therapy

### What are the contraindications for BCG administration?

- Absolute
  - gross hematuria
  - UTI or asymptomatic bacteriuria (not sure how much cystitis actually present)
  - traumatic catheterization
  - immunosuppression and immunocompromised pts: HIV, transplant pts, leukemia, lymphoma
  - recent TURBT
- Relative
  - poor overall performance status
  - advanced age
  - active TB or prior hx of TB: higher incidence of side effects, less efficacy

## Chapter 77 Questions - UCC Superficial.doc

- previous severe reaction to BCG
- prosthesis
- pregnancy and lactation
- heart valve

### How well does BCG work in pts w/ CIS?

- initial tumour-free RR 76%
- 50% durable response for median period of 4 years
- 30% tumour-free over 10 years

### How well does BCG work after radiation?

- about the same
- no increased risk

### What is the risk of progression after BCG treatment?

- responders to BCG: 20% progression at 5 yrs
- persistent disease after BCG: 95% progression at 5yrs

### What response to BCG dictates the need for more aggressive treatment?

- failure to respond to 2 6-week courses of BCG
- early recurrence of high-risk disease

### How well does BCG work in prophylaxis after TURBT?

- **decrease in recurrence of 40% overall** (compared to 15% decreases w/ other intravesical therapies)
  - T1G3 lesions: recurrence 16-40%, progression in 5-40%
- evidence of **delayed progression not definitely established**
  - progression in BCG pts vs. controls: 4% vs. 17%
  - SWOG comparison of doxorubicin and BCG: progression in 37% doxo vs. 15% of BCG
- delay in interval progression of BCG pts vs. TUR controls: Herr (1988)
  - less evident on long-term follow-up
- decreased cystectomy rate for CIS pts (11% vs. 55%)

### What is the "6+3" regimen for BCG?

- SWOG: 6-week induction course, then 3 weekly instillations at 3 and 6 months, then q6months x 3 years
  - **Lamm (2000): recurrence-free survival 6.5yrs in maintenance vs. 3yrs in nonmaintenance**

### What is the benefit of a 2<sup>nd</sup> 6 week induction course of BCG?

- additional response in:
  - 25% pts treated for prophylaxis
  - 30% pts treated for CIS
- increased risk of progression in 20-50%

### What is the role for BCG dose reduction?

- decrease in toxicity w/ no difference in efficacy
- lengthening dose interval has also been studied in some pts: same effect

### How do quinolones affect BCG treatment?

- effective in killing BCG mycobacteria
  - may treat systemic side effects
  - should not decrease efficacy

### What are the side effects of BCG and how are they treated? (J.Urol 147:596)

- Local
  - LUTS, dysuria: usually starts 2-4h post tx, resolves spontaneously within 6-48h
    - hold BCG until sx resolve
    - tx w/ anticholinergics (Ditropan), Tylenol, Pyridium, NSAIDs
    - dose reduction
    - INH x3d then BCG
    - if prolonged >48 hr: INH 300 mg OD while sx persist, then reinstitute 1 day prior to subsequent BCG, continue x3 days

## Chapter 77 Questions - UCC Superficial.doc

- change to another Rx
- cystectomy
- UTI
  - tx w/ antibiotic and hold BCG
- hematuria: hold BCG
- granulomatous prostatitis: 20-30%
  - may progress to testicular involvement: tx w/ orchiectomy if untreated
  - may require INH if severe
- epididymitis/testicular involvement: may need orchiectomy if don't treat
- bladder contracture: hold BCG, hydrodistend, augment
- ureteric obstruction: INH 300mg PO OD x 3-6mo
- renal abscess (if VUR present): rifampin 600mg PO OD x 6mo
- Systemic
  - skin rash, arthralgias, pruritis
    - stop BCG
    - INH 300mg PO OD x 3mo
  - N/V
  - fever/malaise
    - if T > 38.5 for 24 hrs or T > 39.5, tx w/ INH 300mg PO OD x 3 months
  - systemic BCGosis: tx w/ INH 300mg - RIF 600mg for 6 mo, add ethambutol 1200mg if acutely ill
    - manifests as pulmonary or hepatic disease
  - BCG sepsis: tx w/ standard life support + triple drug therapy
    - cycloserine 250-500mg OD → quickest acting
    - Prednisone, quinolones useful when added to drug regimens
  - rare complications
    - immune complex glomerulonephritis
    - choroiditis/ ocular reactions
    - nephrogenic adenoma
    - cardiac toxicity
    - suppurative lymphangitis
    - mycotic aneurysm
    - lupus vulgaris

### What is mitomycin C?

- cross-linking agent that inhibits DNA synthesis
- sensitive in G1 phase, overall non-cell-cycle specific
- instilled weekly for 6-8 weeks at 20-60mg

### How effective is mitomycin C?

- average complete response rate 35%, **decrease in recurrence** from 20-40%
- average benefit 15% in 5 papers, w/ only 2/5 demonstrating statistical significance
- **mitomycin C vs. TUR: no decrease in progression**

### What are the side effects of mitomycin C?

- chemical cystitis: UTI is contraindication to mitomycin
- decreased bladder capacity
- palmar desquamation
- skin rash: avoid skin contact
- leukopenia: rare, due to high MW
- bladder contraction and mural calcification: rare
- nephrotoxicity

### What is doxorubicin and how does it work?

- anthracycline antibiotic
- binds DNA base pairs, inhibiting topoisomerase II and inhibiting protein synthesis
- greatest effect at S phase of cell cycle, but is cell-cycle nonspecific

### How well does doxorubicin work?

- 15% improvement over TUR in preventing recurrence
- **no advantage in preventing progression**



## Chapter 77 Questions - UCC Superficial.doc

What are the side effects of doxorubicin?

- chemical cystitis – main s/e
- decreased bladder capacity
- GI or allergic reactions
- cardiomyopathy, cardiotoxicity
- alopecia
- stomatitis

**What is epirubicin?**

- derivative of doxorubicin
  - 50-80 mg/mL, over 8 weeks
  - decreases recurrence vs. TURBT alone by 15%

**What is thiotepa?**

- alkylating agent: triethylenethiophosphoramide
- non cell-cycle specific

**How well does thiotepa work?**

- decreases tumour recurrence by 15% (up to 40%)
- **no effect on tumour progression**

**What are the side effects of thiotepa?**

- myelosuppression (leukopenia): low MW
- thrombocytopenia → contraindication to thiotepa
- LUTS

**What is valrubicin and how does it work?**

- semisynthetic analogue of doxorubicin
- causes cell-cycle arrest in G2 phase and inhibits topoisomerase II

**What is the role of valrubicin?**

- treats BCG refractory CIS who cannot tolerate cystectomy

**What is ethoglucid?**

- triethyleneglycol diglycidyl ether
- podophyllin derivative
- alkylating agent
- give as 1% solution q weekly x 4-10 weeks
- decreases recurrence rate, no evidence to show decrease in tumour progression
- s/e: urgency and frequency, allergic skin reaction

**What combinations of chemotherapy have been used to treat UCC?**

- mitomycin C (20mg) on day 1, doxorubicin (40mg) on day 2
  - q weekly x 5 weeks
  - 50% CR
  - **significant s/e in 50%**
- combination chemo + BCG
  - T1 or Ta lesions: no difference in recurrence, progression, or s/e in pts treated w/ BCG + mitomycin vs. mitomycin alone
  - Tis lesions: may have advantage in progression and DFI

**What is the theoretical advantage to immediate instillation of chemo after TURBT?**

- may hinder tumour reimplantation
- immediate therapeutic efficacy for microscopic residual disease
- no way to stratify pts into who gets immediate adjuvant intravesical chemo → either all pts or none

**What results are available for immediate instillation of chemo after TURBT?**

- TUR alone vs. 1 immediate dose mitomycin C vs. mitomycin C x 5 weeks q3mo
  - single dose: **decreased RR by 50%, increases recurrence-free interval**

## Chapter 77 Questions - UCC Superficial.doc

→ trend towards additional improvement w/ further doses (not SS)

### What forms of immunotherapy have been used to treat UCC?

- interferon: glycoproteins produced in response to antigenic stimuli → multiple antitumour activities: stimulates cytokine release  
→ effective in eradicating residual disease w/ 20-45% CR
- keyhole-limpet hemocyanin (KLH):  
→ copper-containing antigenic protein from the hemolymph of *Megathura crenulata*, a mollusk  
→ is a non-specific immunostimulant → less effective than BCG, but is less toxic
- bropiramine  
→ is an arylpyridinone, induces IFN → not available
- thiosulfinate extracts of garlic
- IL-12, IL-2

### What is involved in UCC surveillance?

- Ta, T1 intermediate grade → TURBT  
→ routine cystoscopy, UA, cytology  
→ IVP q 4yr (2-3 yrs if recurrence)
- CIS, TIG3, multifocal disease → TURBT + BCG  
→ routine cystoscopy, UA, cytology  
→ IVP q 1-2 yrs  
→ cystectomy vs. repeat BCG if recurrence

### What is the rate of upper tract recurrence after treatment of superficial bladder UCC?

- 0.002-2.4%, usually w/i 5 years  
→ 1% in low-risk pts (low-grade, Ta/T1), 2% in intermediate risk (recurrent/multifocal), 10% in high-risk (CIS, BCG failures)
- **upper tract recurrence usually lethal: 40-70% mortality**
- at risk for prostatic UCC recurrence

## New Therapeutic Strategies for Superficial Bladder Cancer – AUA Update XXII #2

### What is the evidence that shows superiority of BCG vs. mitomycin C in recurrence of UCC?

- 4 comparative mitomycin-BCG trials show BCG superiority, 3 trials show therapeutic equivalence

### What options are available to decrease tumour recurrence upon 1<sup>st</sup> presentation of tumour?

- improved visualization of all tumour w/ 5-ALA cystoscopy
- re-resection for larger tumours / high grade / T1

### How often does conventional cystoscopy miss UCC?

- up to 33%

### What options are available to prevent recurrence at the time of TURBT?

- perioperative cytotoxics  
→ clinical advantage in perioperative intravesical chemotherapy for all stages and grades of primary/secondary papillary ca  
→ best results if give w/i 2 hrs of TURBT, lose effectiveness if not given w/i 24 hrs
- cytostatic/cytotoxic oral agents
- modified irrigant solutions  
→ sterile water washout post-op: osmotically unfavourable to tumour cells

### How can one optimize the effectiveness of intravesical chemotherapy?

- optimize chemotherapeutic pharmacology  
→ inducing relative dehydration  
→ removing all residual urine at the time of instillation  
→ decreasing the volume (but not dose) of diluent of mitomycin C  
→ increasing urinary pH from 5 to 7 to stabilize mitomycin C
- combining chemo w/ synergistic technologies  
→ combine chemo w/ hyperthermia via intravesical microwave tx
- modify intrinsic chemosensitivity

## Chapter 77 Questions - UCC Superficial.doc

- decrease resistance of tumour: alter MDR efflux pump, FGF-mediated resistance, quinone reductase drug activation
- alternative chemotherapeutic agents and multi-agent chemo
  - not beneficial yet w/ intravesical agents

### What was the only trial to demonstrate statistically significant benefit to maintenance BCG?

- SWOG 8507
  - randomized BCG responders at 3 mo to 3wk maintenance courses at 3, 6, 12 months and q6mo x 3 yrs
  - 5yr disease-free survival improved from 40 to 61%, freedom from progression increased from 70 to 76%
  - pts w/ CIS: CR increase from 68 to 84%
  - only 16% of pts randomized to maintenance actually received all scheduled treatments
    - ½ falling off after the 3<sup>rd</sup> set of treatments due to intolerance

### What evidence is there that shows whether the dose of BCG can be reduced to minimize toxicity?

- several trials: decreasing BCG dose to ½ or 1/3 in induction phase will lower toxicity
- controversial if efficacy decreased

### What are the AUA Guidelines for the management of superficial bladder cancer?

- decision making differences based on specific pt circumstances that are reflected in recommendations for 3 different index pts
- discuss tx options and benefits and harms, including s/e of intravesical treatment
  - #1: pt w/ abnormal growth in bladder, but not yet dx w/ bladder ca
    - Standard: biopsy must be obtained for pathology
  - #2: pt w/ established bladder cancer of any grade, Ta or T1, +/- CIS, who has not had any prior intravesical chemo
    - Standard: complete eradication of all visible tumours if surgically feasible and if pts medical condition permits
      - ◆ may be done by any method: electrocautery resection, fulgurization, or laser ablation
      - ◆ adjuvant intravesical chemo is an option after removal of TaG1 lesions
    - Guideline: intravesical instillation of BCG or mitomycin C is recommended for tx of CIS and after TUR of T1 (any grade) or TaG3 lesions
    - cystectomy may be considered for initial therapy in some pts w/ CIS or T1 lesions
  - #3: pt w/ CIS or high-grade T1 UCC w/ at least 1 course of intravesical chemotherapy
    - cystectomy or further intravesical chemotherapy may be considered if CIS or T1 lesions persist after initial intravesical chemotherapy



## Chapter 78

### • **Management of Invasive and Metastatic Bladder Cancer** •

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#### **What are the presenting sx of invasive bladder ca?**

- same sx as superficial ca
  - hematuria: micro or gross → 80%
  - LUTS
  - constitutional sx: metastatic disease

#### **What investigations are involved in the diagnosis of invasive UCC?**

- TUR of bladder lesion
- restaging TUR
  - reduction of stage to pT0 by 2<sup>nd</sup> TUR: improved survival
- **examination under anaesthesia (EUA) → don't forget!**
  - palpable mass correlates w/ stage T3
- axial imaging
  - prior to TUR if suspect invasive lesion

#### **What are the various ways one can stage bladder ca, and their accuracy?**

- CXR, LFT, Ca profile, ALP
- CT
  - cannot identify microscopic extravesical extension
  - correlation of CT findings in 65-80%
  - detects LN mets in 50-85%
- MRI
  - accurate staging in 70%
- bone scan
  - used for pts w/ sx suggestive of bone involvement
  - not needed for pts w/ clinically organ-confined, muscle-invasive bladder ca
- PET scanning
  - based on uptake of fluorodeoxyglucose (FDG) by tumour cells
- laparoscopy
  - concern re: port site recurrence

#### **What are the indications for radical cystectomy?**

- radical cystec in male, plus anterior exent in female, + en bloc pelvic lymphadenectomy
  - for muscle-invasive bladder ca in absence of mets
  - incomplete or difficult re-resection
  - BCG failures
  - prostatic stromal involvement
  - young pts: in 15 yrs, many pts will relapse

#### **What are the tx options for invasive UCC?**

- active surveillance after aggressive TUR
- partial cystectomy
- radical cystectomy
- radical rads
- neoadjuvant chemo
- preop rads
- adjuvant chemo
- systemic tx for metastatic disease

#### **How should one deal with the urethra in muscle-invasive UCC?**

- Male urethra

## Chapter 78 Questions - UCC Invasive.doc

- 43% male urethral (prostatic) involvement in UCC
  - significantly associated w/ presence of CIS in BN or trigone
- **increased incidence of anterior urethral involvement in men w/ prostatic stromal involvement**
  - 64% if stroma, 25% if ducts, 0% if urothelium
- pts undergoing continent diversion should have simultaneous/delayed urethrectomy if **CIS or gross tumour involvement of prostatic urethra**
- orthotopic diversion: cannot commit to using native urethra until get **frozen section of urethra at time of OR**
- Female Urethra
  - 2-12% of female urethras involved w/ UCC
  - presence of ca at BN correlates w/ presence of urethral ca

### What are the indications for urethrectomy?

- Absolute
  - gross carcinomatous involvement of the urethra
  - UCC of prostatic stroma: **5-yr survival for pts w/ prostatic stromal invasion is 40%**
  - +ve margin at time of OR
  - urethral recurrence post-cystectomy
- Relative
  - solitary tumour at BN: urethrectomy required in only 4%
  - diffuse CIS of bladder
  - multifocal bladder tumour
  - large bladder tumour
  - unreliable pt
  - female pt
  - SCC
  - CIS of prostatic urethra

### What are the contraindications to orthotopic reconstruction in the female pt w/ invasive UCC?

- overt cancer at the BN and urethra
- diffuse CIS
- +ve margin at surgery

### How does one deal with the ureteral margins at the time of cystectomy?

- ureteral frozen section at time of OR
  - CIS can involve distal ureteral margin
  - retrospective studies have failed to show that clearing the ureteral margins at cystec provides long-term benefit

### Describe the long-term disease-free survival by stage after cystectomy.

- **pT2: 60-80% → long term survival uniformly better in pts w/ pathologically organ confined disease**
- pT3: 30-50%
- pT4: 20-40%

### What is the role of pelvic lymphadenectomy in radical cystectomy?

- provides insight into local extent of disease
  - limited nodal burden = high rate of long-term survival
  - obturator and external iliac chains are most commonly involved
- the more nodes out, the better: may cure some pts w/ LN mets: Jewett, 2004
- extended lymphadenectomy: includes common iliac, presacral, up to IMA
  - based on JCO (Skinner data)

### What is the risk of +ve LN at the time of cystectomy?

- risk of pelvic LN mets increases w/ stage
  - pT2 disease have 10-30% risk of +ve LN at time of surgery
  - pT3-4 disease have 30-65% risk of +ve LN at time of surgery

### What are the complications of radical cystectomy?

- overall rate 25-35%
- complications associated w/ the anaesthetic/intubation
  - allergic reaction
  - MH

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- respiratory complications: atelectasis, others
- complications associated w/ preexisting conditions
  - MI, cardiac arrest
  - DVT/PE
  - arterial thromboembolism/stroke
- complications associated w/ removal of bladder and adjacent structures (intra-op complications)
  - hemorrhage, post-op pelvic hematoma
  - rectal injury
    - RF: radiation, previous pelvic surgery, extensive TUR of bladder floor, IBD
  - vascular injury
  - urine leak
  - fistulae
- complications from use of GI segments for diversion (post-op complications)
  - infectious complications
    - wound infection
    - sepsis
    - pelvic abscess
    - pneumonia
    - pyelo
    - cholecystitis
  - ileus, bowel obstruction
  - pancreatitis
  - ureteral-enteric anastomotic strictures: 3%, more common if do non-refluxing reimplant
  - metabolic disorders
  - vitamin deficiencies
  - chronic UTI
  - renal calculous disease
  - stomal problems: stenosis, parastomal hernia
- other: depression, incisional hernia, gout, thrombocytopenia, wound dehiscence, ED, tumour recurrence

### What is the treatment of a rectal injury during cystectomy?

- recognition of injury is key
  - if uncertain, may place red rubber in rectum, fill pelvic w/ water, inject air into rectum, look for bubbles
- decision b/w primary repair +/- colostomy
  - **colostomy is considered standard of care**
    - perform in pts w/ gross spillage, previous radiation, inadequate bowel prep
    - mucosa closed w/ 3-0 absorbable suture, outer layer w/ 3-0 silk
    - irrigate pelvis w/ water/antibiotic solution
    - place omentum/fat over repair
  - post-op antibiotics
  - consider pelvic drains
  - manual dilation of anus
  - consider consult from general/colorectal surgery
- factors: pt age, comorbidities, nutritional status, previous treatment, quality of bowel prep, size of injury

### What are the factors that contribute to wound dehiscence?

- infection
- steroid use
- radiation
- poor nutrition
- pulmonary disease
- surgical technique

### Describe the follow-up after radical cystectomy.

- no standard of practice
- pT1: annual exam
  - exam
  - blood work
  - CXR
  - upper tract imaging to exclude stricture or recurrence

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- pT2: biannual exam
- pT3: quarterly exam
  - add CT q6mo

### What is the natural hx of pts after radical cystectomy for invasive UCC?

- Stein (2001) JCO
  - 1054 pts treated w/ cystectomy for UCC from 1971-97
  - recurrence-free survival 68-66% at 5 and 10 yrs
  - pts w/ < 5 LN +ve or non-organ confined disease have significantly lower survival rates
  - recurrence in 30%: median time to recurrence 12mo

### What is the role of neoadjuvant radiation for invasive UCC?

- for T3 disease, may help w/ local control
  - survival advantage difficult to demonstrate

### What are the advantages and disadvantages of neoadjuvant chemotherapy for invasive UCC?

- Advantages
  - allows for a demonstration of tumour chemosensitivity
  - downstaging of otherwise inoperable lesions
  - treats micromets w/ pt not debilitated by OR
- Disadvantages
  - error resulting from reliance on clinical and not pathologic staging
  - delay in delivery of definitive local therapy

### What is the role of neoadjuvant chemotherapy?

- 7 phase 3 RCT studies, 5 show no difference in outcome
  - platinum based chemo

### Does neoadjuvant chemo before radical therapy improve survival in T2-4 bladder cancer?

- Perhaps....
  - Neoadjuvant chemo + cystectomy vs. cystectomy alone for locally advanced bladder cancer. Grossman, NEJM, 2003
    - 317 pts w/ stage T2-T4a bladder cancer, variety of urinary diversions created, receiving 3x28d cycles of MVAC
    - median survival: 46 months for surgery alone, 77 months for chemo pts
    - but.... total % survival not much different at a given time point → larger % die early on, then similar after 1-2 years
  - Neoadjuvant chemo in invasive bladder cancer. ABC Meta-analysis. Lancet, June 7, 2003.
    - Question: Does neoadjuvant chemo increase survival in invasive bladder cancer?
    - Method: 10 randomized trials, 2688 pts – meta-analysis.
      - ◆ pts had neoadjuvant chemo + cystec/rads/rads+cystec
    - Results
      - ◆ platinum based chemo showed benefit to overall survival
      - ◆ 14 trials: 3 ineligible, 1 unavailable
      - ◆ single agent platinum: HR of 1.15, absolute benefit of –5% at 5yrs → few studies
      - ◆ combination chemo: HR of 0.87, 13% RR in risk of death, absolute benefit of 5% at 5yrs, improving survival from 45% to 50%
        - ◆ benefit on overall survival, disease-free survival, locoregional disease-free survival, mets-free survival
      - ◆ local tx (cystectomy, rads, or cystec + rads) not significant

### What is the role of perioperative chemotherapy?

- MD Anderson 1996
  - 100 pts randomized to 2 cycles of MVAC before and 3 after vs. 5 cycles after OR
  - no difference in survival

### What is the role of adjuvant chemotherapy?

- Advantages
  - pathologically staged pts w/ mets can benefit from systemic therapy to reduce risk of recurrence
- Disadvantages
  - delay in delivery of systemic therapy to pts w/ mets
  - difficulty of assessing tumour response w/o radiographically demonstrable disease

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- post-op complications preventing completion of tx
- reduced pt compliance after major OR

### What is the evidence for adjuvant chemo after cystectomy?

- Randomized trials: Skinner, Stockle, Studer, Freiha
  - all were small studies
  - cisplatin-based adjuvant tx may provide survival benefit in selected pts w/ regional disease and +ve pelvic LN
  - not useful for pts w/ T1-2 disease only
- Skinner: Role of chemotherapy for invasive UCC (1991) J Urology
  - 500 pts, only 91 randomized w/ T3-4 disease +/- LN involvement: 44 got PAC x 4 cycles, 47 cystectomy only
  - delay in progression: 70% of chemo pts free of disease at 3 yrs, vs. 46% of cystectomy only group
  - increased survival in chemo pts: 4.3 vs. 2.4 yrs
    - only 64% got 4 cycles of chemo, rest got < 4, and only 33/44 got any chemo
    - no T2 disease, old study, pre-MVAC → not applicable any more
- Stockle: Cystectomy +/- adjuvant MVAC for T3b/T4a UCC (1996) Urology
  - 166 pts undergoing cystectomy: 80 received 3 cycles of adjuvant MVAC, 86 cystectomy only
  - worse survival w/ increasing LN involvement in both groups
  - significant prolongation of relapse-free survival in MVAC group

### What are the alternatives to standard tx in invasive disease?

- radiation therapy
  - no randomized trials compare rads w/ cystectomy
  - controls locally invasive tumour in 30-50%
- interstitial radiation
  - overall survival rates 60-80% for T1-2 lesions
  - 98% probability of bladder preservation
- TURBT +/- chemo
  - may be useful for small, well-defined superficially invasive bladder cancers (T2)
  - results may be similar to cystectomy in selected pts
- partial cystectomy +/- chemo
  - use radiation (40-65Gy) + chemo (cisplatin, MVC, MVAC, C/5FU)
  - F/U 2-6.5 yrs, 50-80% CR, 35-90% bladder preservation
- bladder-preservation protocols
- intra-arterial chemotherapy
  - increased local dose to tumour
- hyperthermia and chemotherapy

### What are the results of T2 UCCs treated w/ radical TUR alone?

- Herr (2001) J Clin Oncol
  - 432 pts w/ T2 disease that received reTURBT
  - 281 had residual T2 disease and got cystectomy, 151 pts had T0-T1 → 52 had cystectomy, 99 were observed (73 T0, 26 T1)
  - 76% of 99 pts had 10 yr disease specific survival in pts observed vs. 71% of 52 pts in immediate cystectomy group

### What are the pros and cons of bladder preservation protocols in invasive bladder ca?

- Pros
  - pts w/ T2 disease may have micromets at presentation, so no benefit to cystectomy
  - removal of bladder not necessary in asymptomatic pt, no increase in QOL, and delays definitive chemo
- Cons
  - preservation protocols rely on clinical and not pathologic staging: error to tx
  - local recurrence and complications: failure to control local lesion
  - orthotopic bladder reconstruction is widely available

### What are the results from bladder sparing protocols in invasive UCC?

- no prospective randomized data available
- Sternberg (1999) Ann Oncol
  - 87 pts w/ T2-T4a UCC tx w/ 3 cycles of neoadjuvant MVAC
    - 42 pts received TURBT: 50% T0 at TURBT, 70% alive (most w/ bladder)
    - 13 partial cystectomy: 60% alive w/ bladder
    - 32 pts radical cystectomy: 63% alive



## Chapter 78 Questions - UCC Invasive.doc

### What are the contraindications to bladder-sparing protocols?

- hydronephrosis
- CIS
- tumour that cannot be completely resected w/ TURBT

### What are the complications of interstitial therapy?

- delayed wound healing
- fistula formation
- hematuria
- chronic cystitis

### What are the commonly employed agents to treat metastatic/locally advanced bladder ca?

- MVAC: methotrexate, vinblastine, doxorubicin (adriamycin), cisplatin
  - superior to single-agent tx as well as CAP
  - CR in 20%
  - significant toxicity: neutropenic fever in 20%, death from sepsis in 3-4%
  - dose escalation w/ bone-marrow supportive agents: GM-CSF (Neupogen)
  - long-term disease free survival rate only 3.7% at 6 yrs (Saxman, 1997 JCO)
- gemcitabine (Gemzar)
  - similar survival b/w GC and MVAC, but GC is more tolerable and safer (von der Maase, JCO 2000)
  - antimetabolite: analogue of cytosine arabinoside (ara-C)
  - 25% CR alone
  - 40% PR and CR w/ cisplatin
- taxoids
  - microtubule disassembly inhibitors
  - paclitaxel (Taxol) and docetaxel (Taxane): RR 25-83%
- gallium nitrate
  - naturally occurring metal: 10-50% RR → significant toxicity
- trimetrexate
  - antifolate

### What are the results after salvage cystectomy for residual disease after local therapy?

- 22% survival in pts w/ complete or near-complete response to systemic therapy

### What are the s/e from MVAC?

- neutropenia and its infectious complications: 20%
- mucositis: difficulty eating/drinking → weight loss and weakness
- N/V
- cardiac
- renal
- neurologic toxicity
- death 3-4%

### What are the s/e from Gem/Cis?

- neutropenia and its infectious complications: 10% → less compared to MVAC
  - sepsis
- mucositis: less compared to MVAC
- death 4%

### How does a continent diversion affect adjuvant chemo?

- increased absorption of MTX through pouch
  - place Foley in pouch during chemo

### What is MTX?

- methotrexate: dihydrofolate reductase inhibitor
  - cell cycle specific for S-phase
- side effects
  - BM
  - NVD

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- stomatitis
- hepatotoxicity
- pulmonary toxicity (leucovorin minimizes)
  - leucovorin = active form of B complex folate
  - used in pts that have depleted folate
- ARF (alkalinize urine and hydrate)

### What is cis-platinum?

- non cell-cycle specific alkylating agent
- side effects
  - BM suppression
  - NV
  - ototoxicity (high freq hearing loss)
  - nephrotoxicity: force hydration, avoid gent, NOT with CRF
  - alopecia
  - Mg leak with seizures
  - Ca leak
  - neurotoxic
  - Raynaud's
  - anaphylaxis
  - 2<sup>nd</sup> malignancy
  - hypercholesterolemia
  - hyperuricemia





## **Chapter 79**

### **• Surgery of Bladder Cancer •**

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#### **What is the mortality rate for cystectomy?**

- 1-3% in most contemporary series

#### **What approaches are available to reach the bladder?**

- Vertical – easier to perform
  - midline: lap, minilap
  - paramedian
- Horizontal – more cosmetic
  - Pfannenstiel: transverse incision 1-2cm above pubis
    - divide anterior rectus fascia transversely, and upper and lower fascia flaps are dissected off, divide rectus in midline
  - Cherney: higher than Pfannenstiel, also transverse
    - divides rectus sheath and rectus muscles transversely

#### **What is involved in the preop evaluation for TURBT?**

- Hx: past/current smoking, occupational exposure
- Px: bimanual exam
- Ix
  - imaging: IVP, CT, US, retrograde
  - micro: urine C&S
  - labs: CBC, lytes, Cr, coags

#### **Describe the surgical technique for TURBT.**

- lithotomy position
- GA w/ paralysis
- panendoscopy
  - location and number of tumours
  - location and efflux from both UOs
- Irrigant:
  - water if short case
  - if long case: glycine, sorbitol, mannitol → may reduce risk of hemolysis
- if lesion is small: cold-cup bx and fulguration
- Loops: finer loops concentrate current and cut more easily, larger loops provide better hemostasis
- Current:
  - cutting: best for cutting is undamped current generated by a tube oscillator circuit
  - coag: best w/ highly damped spark-gap current generated by a spark-gap oscillator circuit
  - blended
- resect most exophytic region of tumour first, beginning at most anterior or superior portion
- if first TURBT and multiple tumours, try to resect all: otherwise may fulgurate
- Postoperative Management
  - Foley drainage: remove w/ hematuria resolved → next morning
    - prevents bladder from needing to empty w/ contraction: prevents bleeding
  - no antibiotics required
  - PO analgesia, antispasmodics

#### **What patients w/ T2 disease are may be candidates for TUR therapy alone?**

- small, solitary, papillary moderately differentiated stage T2 or minimal stage T3a lesions
- smaller than 2cm in diameter at base
- lesion must be completely resectable transurethrally
  - **must get –ve biopsies at base of tumour at end of TURBT**

## Chapter 79 Questions - UCC OR.doc

### How well do pts w/ T2 bladder ca w/ TUR therapy alone?

- 10% of pts w/ T2 disease are pT0 at cystectomy
  - no studies have compared TURBT alone vs. cystectomy
- Solsona 1992: selected cases of T2 bladder ca (initial resection complete, -ve bx at end of case)
  - 59/308 pts had T0 disease on repeat TURBT
  - 83% 5yr survival, 50% tumour-free

### What are the complications of TURBT?

- bladder perforation/obturator nerve spasm +/- tumour seeding
  - **perform intraoperative cystogram**
  - extraperitoneal: may require drain if large
  - intraperitoneal: may require formal exploration and repair, esp. if large → r/o bowel injury
- hematuria and clot retention
  - hand irrigation: return to cysto if doesn't resolve
- volume overload: fluid restrict
- electrolyte imbalance
- intravascular hemolysis → renal failure: treat w/ diuretics
- obstruction of ureteric orifice: unlikely if use only cutting current across orifice
- urethral strictures

### Describe the operative technique for radical cystectomy in the male.

- Preoperative Evaluation and Management
  - stop ASA 2wks prior
  - stop smoking
  - hx/px, bimanual
  - **stage w/ TURBT, bladder/urethral biopsies**
  - CT pelvis/abdomen
  - CXR
    - CT chest if needed
  - CBC, lytes, LFTs
    - bone scan if needed
  - GI workup: barium enema/colonoscopy if pre-existing GI disease → may affect diversion
  - autologous blood
  - Fe gluconate 300mg PO TID
  - perioperative SC heparin
  - bowel preparation: may need to admit pt day before for prep
    - CF x 2days prior to OR
    - GoLYTELY day prior
    - neomycin and erythromycin base 1g TID day prior
- Operative Technique
  - Incision
    - table flexed
    - 22F Foley
    - midline lower abdo incision
    - develop space of Retzius
    - open peritoneal cavity, perform full laparotomy for mets
      - ◆ confirm position of NG tube
    - urachus identified and ligated below the umbilicus
    - incise peritoneum along each side of bladder
    - identify vasa lateral to the bladder and are ligated and divided
    - divide colonic adhesions
    - packs in each colonic gutter
  - Bilateral pelvic lymphadenectomy
    - medial to genitofemoral nerve (lateral limit to dissection)
    - external iliac artery and vein dissected to bifurcation of common iliac (cephalad limit)
    - endopelvic fascia (caudal limit)
    - bladder (medial limit)
    - node of Cloquet mobilized at junction of femoral canal
  - Cystectomy
    - divide branches of the hypogastric artery, but the artery itself is not divided

## Chapter 79 Questions - UCC OR.doc

- ◆ will compromise blood flow to internal pudendal (vasculogenic impotence)
- ureters identified and divided close to the bladder
- ureteric margins sent for frozen
- posterior peritoneum incised
- plane b/w bladder and rectum is developed
- endopelvic fascia incised and puboprostatic ligaments are divided
- dorsal complex is divided and oversewn
- urethra divided
  - ◆ frozen section of urethra if continent diversion
- pass heavy ligature around urethra and tie it at level of apex of prostate to prevent leakage of urine after urethral division
- divide vascular pedicles, remove specimen
- Diversion
- Postoperative Management

### What structures are removed in a radical cystectomy in a male and in a female?

- Male
  - Bladder and distal ureters
  - Prostate
  - Seminal vesicles
  - Ampullae of the vas
  - Pelvic lymph nodes
  - Perivesical fat and peritoneal reflection
  - Urachus
  - +/- Urethra with meatus if indicated
- Female
  - Bladder and distal ureters
  - Pelvic lymph nodes
  - Perivesical fat and peritoneal reflection
  - Urachus
  - Uterus
  - Fallopian tubes
  - Ovaries
  - Anterior 1/3 of vagina
  - Usually urethra with meatus

### What is the rate of urethral recurrence of TCC after cystectomy?

- 4-18%
  - highest in pts w/ prostatic stromal invasion (20-65%) or ductal/urethral involvement (15-25%)

### What are the indications for urethrectomy?

- Absolute
  - carcinomatous involvement of the urethra
  - TCC of prostatic stroma: **5-yr survival for pts w/ prostatic stromal invasion is 40%**
  - +ve margin at time of OR
  - urethral recurrence post-cystectomy
- Relative
  - solitary tumour at BN: urethrectomy required in only 4%
  - diffuse CIS of bladder
  - multifocal bladder tumour
  - large bladder tumour
  - unreliable pt
  - female pt
  - SCC
  - CIS of prostatic urethra

### Describe the operative technique for urethrectomy.

- Operative Technique
  - exaggerated lithotomy
  - before cystectomy, divide dorsal vein: suture w/ 3-0 absorbable

## Chapter 79 Questions - UCC OR.doc

- pass ligature around urethra and ligated to prevent spillage of tumour from bladder
- divide NVB away
- dissect urethra into UGD and transected
- remove cystoprostatectomy
- frozen section of urethra sent
- 26F Van Buren sound passed
- inverted-Y incision from base of scrotum towards anus
- bulbocavernosus divided in midline
- Penrose placed around urethra
- urethra dissected from each cavernosa
- penis inverted, urethra dissected towards glans
- dissected carried into glans
- carefully dissect into areas posterior and lateral to bulb: expose and clip bulbar urethra arteries
  - do not fulgurate: may injury internal pudendal arteries
- irrigate w/ antibiotic solution
- JP drain
- bulbocavernosus muscles reapproximated
- subcutaneous layer closed
- skin closure w/ 4-0
- Postop Management
  - drains removed in 1-2d

### Describe the preoperative management and operative technique for radical cystectomy in the female.

- Preop
  - Hx: smoking, chemical exposure, other RF
  - Px: bimanual exam
  - Ix:
    - Labs: CBC, LFT
    - Radiology: CT chest, abdo, pelvis
    - bone scan: only if abnormal ALP or other sx of mets
  - Bowel prep
    - GoLYTELY
    - antibiotics
    - enema
  - stomal therapist consult
- Surgical Technique
  - Foley
  - midline incision to L of umbilicus
  - retroperitoneal space entered
  - peritoneum mobilized off transverse fascia
  - urachus umbilicus ligaments are ligated and divided
  - peritoneum opened
  - palpation to exclude occult mets in abdo/pelvis, liver
  - peritoneum lateral to the bladder incised
  - round ligament ligated and divided
  - ovarian vessels in infundibulopelvic ligament are identified, ligated, and divided
  - Pelvic lymphadenectomy
    - genitofemoral nerve identified and preserved
    - nodal pack: start over external iliac, beginning at junction of hypogastric artery and external iliac artery
    - carry down to pelvic sidewall to obturator NVB
  - Pelvic dissection
    - dissection down hypogastric artery
    - initial anterior arterial branch is superior vesical artery
    - ureters ligated at UVJ
    - proximal ureters packed away
    - frozen section of proximal ureter
    - ureter spatulated and feeding tube sutured in place
    - vaginal wall mobilized off rectosigmoid colon
    - iodine spongestick in vagina
    - cautery to incise vagina

## Chapter 79 Questions - UCC OR.doc

- if urethrectomy to be performed, identify and cut pubourethral ligaments
- identify and cut dorsal venous complex
- Vaginal dissection
  - ovaries, fallopian tubes, uterus, ant. vagina, and cervix attached only by small portion of anterior vagina and urethra
  - urethral meatus circumscribed if urethrectomy performed
  - vagina reconstructed
  - midline incision closed
- Postop
  - vag pack x 2d
  - drains removed w/ GU tract proven intact radiographically

### What are the contraindications to neobladder in the female?

- +ve frozen section of proximal urethra
- primary tumour at BN

### What are the indications for simple cystectomy?

- pyocystitis
- neurogenic bladder
- severe UI
- severe urethral trauma
- large vesical fistula
- cyclophosphamide cystitis
- radiation cystitis
- severe LUTS after supravescical diversion w/o cystectomy: up to 80%
  - up to 20% require cystectomy
  - simple cystectomy may be performed in pts that undergo irreversible diversion

### What are the complications of retained defunctioned bladders after diversion?

- hemorrhage
- sepsis
- pain
- sensation of incomplete emptying
- fistulae
- pyocystitis
- bladder ca

### Describe the surgical technique of simple cystectomy.

- low midline incision
- develop retropubic space
- sweep peritoneum cephalad
- divide superficial veins on bladder
- divide BN
- carry incision posteriorly to SV
- bladder mobilized off ampulla of vasa and SV
- prostate oversewn w/ 2 layers
- remaining peritoneum dissected off superior bladder
- superior and middle vesical arteries ligated
- specimen removed

### What is the rate of local recurrence for T2 TCC after partial cystectomy?

- 40-80%
  - overall survival 25-55%

### What are the indications for partial cystectomy?

- For TCC bladder:
  - selected pts w/ T2 bladder TCC
    - no CIS/atypia in bladder or prostate
    - normally functioning bladder w/ good capacity
    - 1<sup>st</sup> time recurrence w/ solitary tumour



## Chapter 79 Questions - UCC OR.doc

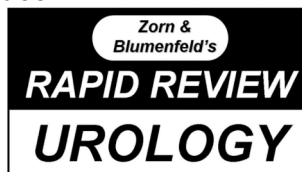
- tumour location in area that allows for 1-2cm margin (dome)
- urachal adenocarcinoma
- primary pheo or osteosarcoma of bladder
- tumour w/i bladder diverticulae
  - often do poorly: higher risk of mets
  - **TCC in diverticulum: combine adjuvant or neoadjuvant chemo + partial cystectomy**
    - ◆ 66% invasive disease free survival at 4 yrs
  - role of rads unknown
- For benign disease
  - leiomyoma
  - fibroma
  - Hunner's ulcers not amenable to TUR
- For bladder invasion from adjacent organs
  - Colon ca
  - Cervical ca
  - Endometrial ca
  - Ovarian ca

### What are the contraindications for partial cystectomy?

- Absolute
  - CIS elsewhere in bladder
  - multifocal tumours
- Relative
  - high-grade tumours
  - tumours that require reimplantation

### What are the complications of partial cystectomy?

- urine leak: most common
  - tx w/ prolonged catheter drainage
- voiding disturbances: if remove large amount of bladder
- wound infection
- hernia
- recurrent disease
  - pts require cysto/cytology q3mo for > 2 yrs
  - CT abdo pelvis regularly



## **Chapter 80**

### **• Management of Urothelial Tumours of the Renal Pelvis and Ureter •**

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#### **Describe the presentation of upper tract urothelial tumours.**

- hematuria: gross or microscopic (75%)
- flank pain/colic (30%) → more common in upper tract tumours
  - dull: gradual obstruction and distension of collecting system
  - acute colic: passage of blood clots
- limb edema: due to ureteral obstruction/renal failure
- pyelo/pyonephrosis
- sx of advanced disease: abdo/flank mass, wt loss, anorexia, anemia, fatigue, bone pain, hepatomegaly
- hydro or nonvisualization on imaging
  - **filling defect: most common finding on imaging**
  - hydro: linked w/ invasion in 80%

#### **Describe the pathologic distribution of upper tract urothelial tumours.**

- 85% of renal pelvis tumours are papillary
  - T1 or T2 in 50% of papillary lesions, 80% of sessile
- **50-60% of renal pelvis tumours are invasive**
- 55-75% of ureteral tumours are low grade and low stage tumours
  - invasion more common than among bladder tumours
- tumours of renal pelvis more common than ureteral tumours

#### **How often do upper tract tumours recur?**

- ipsilateral recurrence in 35-55%: due to multifocal field change

#### **What is the incidence of upper tract tumour after bladder tumour?**

- 2-4%, mean time to occurrence of 70 months
  - upper tract tumours in 3-9% after cystectomy

#### **What is the incidence of bladder tumour after tx for upper tract tumour?**

- 20-75%

#### **What two forms of upper tract urothelial tumours have an extremely high tendency to multiple and bilateral tumours?**

- Balkan nephropathy: low grade
- analgesic abuse

#### **What is the most important determinant of outcome in upper tract tumours?**

- tumour stage

#### **What are the common metastatic sites of upper tract tumours?**

- lungs, liver, bones, and regional LN

#### **What preoperative evaluation is necessary for upper tract tumours?**

- CXR
- abdo CT
- LFTs
- bone scan if necessary: increased ALP, bone pain

#### **Where are the initial LN mets seen in upper tract tumours?**

- **renal pelvis and upper ureteral tumours → para-aortic and paracaval nodes**
- **distal ureteral tumours → pelvic nodes**

## Chapter 80 Questions - Upper tract UCC.doc

### What are the indications for open nephron-sparing surgery for renal pelvis tumours?

- solitary kidney
  - radical NUU and HD still offer the best chance for cure and survival in pts w/ large, invasive, high-grade organ-confined renal pelvis tumour (T2N0M0) in a solitary kidney
- impaired renal function
- synchronous bilateral tumours
- predisposition to form multiple recurrences
  - endemic Balkan nephropathy

### What tumour features favour tumour invasiveness in upper tract tumours?

- large size
- broad base
- nonpapillary pattern

### Describe the surgical technique for open intra-renal surgery for renal pelvis tumours.

- flank/torque position
- flank/thoracoabdominal incision
- removal of 11<sup>th</sup> or 12<sup>th</sup> rib
- open Gerota's posteriorly
- mobilize entire kidney
- renal vessels and ureter isolated w/ vessel loop
- wound packed w/ dry sponges
- renal pelvis and major infundibulae exposed
- curvilinear incision made in renal pelvis
- tumour excised and base is cauterized
- pelvis closed w/ 4-0 chromic
- suction drain
- urinary stent not routinely needed

### What is the risk of tumour recurrence in the ipsilateral renal pelvis after pyelotomy/partial nephrectomy?

- 7-60% → increases w/ grade: Grade 1 (10%), Grade 2 (30%), Grade 3 (60%)

### What is the indication for radical nephroureterectomy?

- large, high-grade invasive tumours of renal pelvis and proximal ureter
  - either organ confined (T1-2 N0) or only locally advanced (T3-4 N0-2 M0)
- medium grade noninvasive tumours of renal pelvis and proximal ureter if large, multifocal, or rapidly recurring
- poor compliance w/ follow-up

### What is the risk of recurrence in a retained ureteral stump after radical nephrectomy for UCC?

- 30-75%

### What is the role for adrenalectomy in NUU?

- usually performed, even though adds little to cure for upper tract UCC
- perform if locally advanced disease

### What are the long-term results after NUU?

- 84% 5 yr survival (51% for simple nephrectomy)

### What are the pros and cons of regional lymphadenectomy for upper tract tumours w/ +ve LN?

- Cons
  - little therapeutic benefit from lymphadenectomy
    - almost every pt w/ LN +ve disease develops early regional mets
- Pros
  - adds little time/morbidity to procedure
  - important for prognosis
  - may occasionally have therapeutic value

### Describe the technique for lap assisted transperitoneal nephroureterectomy.

- Positioning

## Chapter 80 Questions - Upper tract UCC.doc

- supine, ipsilateral hip/shoulder rotated 15 degrees
- Port insertion
  - 3-4 trocars inserted: 3mm trocar under xiphoid for spleen/liver retraction
- Mobilization of colon
  - peritoneum incised along white line of Toldt
  - colon moved medially
  - leave lateral attachments of Gerota's to prevent kidney from moving
- Proximal ureteronephrectomy
  - proximal ureter identified medial to lower pole of kidney
  - renal hilum identified, vessels exposed
  - artery ligated and divided using GI stapling device
  - renal vein divided
  - kidney dissected free inside or outside Gerota's
- Distal ureterectomy
  - open distal ureterectomy w/ excision of bladder cuff
    - low midline Pfannenstiel or Gibson incision
  - lap distal nephroureterectomy
  - cystoscopy w/ fulgurization of UO
    - Bugbee used to cauterize orifice and intramural ureter

### What is the treatment for ureteral UCC?

- if noninvasive (Ta-T1), grade 1-2 tumours:
  - distal: reimplant
  - proximal: NUU if necessary (multifocal, recurrent, diffuse, large)
  - if need for conservative tx: segmental resection
- G3 disease, T2-3 disease (organ confined or w/ minimal nodes): NUU
  - grade 1-2, T2 lesions of proximal ureter or midureter: can offer segmental resection of ureter (esp if nephron sparing needed)

### What are the indications for open segmental ureterectomy and ureterostomy?

- noninvasive grade 1-2 tumours of the proximal ureter or midureter that are too large for endoscopic ablation
- grade 3 or invasive tumours when nephron sparing is a goal: abnormal kidneys
- poor operative risk

### Describe the operative technique for open segmental ureterectomy.

- modified flank position
- angular extraperitoneal incision from tip of 12<sup>th</sup> rib towards pelvis
- ureter identified, mobilized, and secured w/ vessel loops
- ureter ligated 1-2cm proximal and distal to tumour
- ureteral margin sent for frozen section
- regional lymphadenectomy
- ureter repaired
  - max 4cm defect w/ uretero-ureterostomy
  - ureteral ends spatulated and anastomosed w/ 4-0 absorbable
- closed suction drain: don't touch repair

### What are the indications for distal ureterectomy and reimplant +/- psoas hitch or Boari flap?

- tumours in distal ureter that cannot be removed completely by endoscopic means

### Describe the operative technique for distal ureterectomy and reimplant +/- psoas hitch.

- supine position
- prep penis to access catheter
- Gibson/Pfannenstiel or lower midline incision to access distal ureter
- distal ureterectomy as previous
- reimplant
  - only if short segment
  - refluxing vs. nonrefluxing: balance b/w preventing infx/seeding vs. ease of surveillance of upper tract
- psoas hitch
  - anterior cystotomy
  - bladder mobilized upward over iliacs to psoas at level of iliac crest

## **Chapter 80 Questions - Upper tract UCC.doc**

- bladder secured to psoas fascia w/ 2-0 chromic
- avoid entrapment of genitofemoral nerve
- avoid angulation at ureteral hiatus
- anast w/ 4-0 chromic
- closed-suction drain in all cases
- anterior cystotomy closed in 2 layers w/ 3-0 absorbable
- SP cath optional

### **What are the indications for subtotal ureterectomy?**

- multifocal tumours that do not warrant NUU due to grade and stage
  - grade 1-2, stage Ta-T1 tumours of proximal or midureter that are not amenable to complete endoscopic ablation
  - grade 1-2, T2 tumours of proximal ureter or midureter
- nephron sparing surgery

### **What are the results of subtotal ureterectomy?**

- outcome strongly correlates w/ grade and stage
- 5yr survival: 63% for T1, 50% for T2, poor for T3

### **What are the chances of recurrence after conservative tx of ureteral tumours?**

- 33-55%: usually distal to original lesion

### **What are the advantages and disadvantages of a ureteroscopic approach vs. perc/open approaches?**

- Advantages
  - lower morbidity than perc and open counterparts
  - closed system: no risk of tumour seeding
- Disadvantages
  - smaller working channel, limited field of view
  - difficult to access lower pole
  - difficult w/ previous urinary diversion

### **Describe the staging workup for an upper tract UCC/filling defect.**

- suspicion of upper tract UCC
  - filling defect on radiograph
- check creatinine
- renal scan if concerned re: renal fn
- r/o radioopaque stone
  - CT abdo/pelvis
- metastatic workup
  - LFTs
  - CXR PA and lateral: bone scan if necessary
- ureteroscopy w/ biopsy of lesion
  - NUU: high grade/volume, normal kidneys, or poor compliance w/ follow-up
  - conservative therapy: low grade/volume, abnormal kidneys, poor surgical risk

### **Describe the procedure for endoscopic evaluation of an upper tract lesion.**

- cystoscopy
- UO identified and inspected for lateralizing hematuria
- ureteroscope passed, distal ureter inspected
- guide wire passed into upper ureter
- flexible scope passed into upper tract
- NS washing before biopsy

### **What general approaches can be used for endoscopic tumour ablation?**

- bulk excision w/ ablation of the base
  - use cold-cup bx forceps to remove tumour piecemeal to base
- resection of tumour to base w/ loop electrocautery
  - do not attempt to resect deep (beyond lamina)
  - extra care in mid-upper ureter: wall thin and prone to perf
  - avoid circumferential fulguration: high risk of stricture
- diagnostic biopsy followed by ablation w/ laser

## Chapter 80 Questions - Upper tract UCC.doc

→ may need several biopsy specimens if use 3F biopsy cup forceps

### What are the results after ureteroscopic management of UCC?

- overall recurrence rates 30-35%, 45% risk of bladder recurrence
  - NUU rate 7%
- complications rare: perf, stricture,

### What are the major concerns about ureteroscopic management of UCC?

- accuracy of ureteroscopic biopsies
- limitations of biopsies: difficult to assess stage
- promotion of progression or spread of disease to other urothelial surfaces

### What are the potential disadvantages of performing ureteroscopy in pts w/ upper tract UCC?

- risk of ureteral perforation and extravasation of tumour cells
- denudation of ureteral mucosa, facilitating implantation of tumour
- development of ureteral disruption or stricture formation
- pyelo-venous-lymphatic migration of UCC cells after ureteroscopy
- sampling errors: biopsies not adequate for grading
- not all radiographically visible lesions are accessible to endoscopic inspection
- trivial amounts of hematuria may cloud visibility to make inspection impossible

### What are the pros and cons of a percutaneous approach to upper tract UCC?

- Pros
  - good for larger tumours located proximally in renal pelvis or proximal ureter
  - ability to use larger instruments
  - deeper biopsies: more accurate staging
  - avoids limitations of flexible ureteroscopy
- Cons
  - increased morbidity compared to retrograde approach
  - potential for tumour seeding
    - loss of urothelial integrity
    - exposure of nonurothelial surfaces to tumour cells

### What are the indications for an antegrade approach to a tumour of the upper tract?

- acceptable in low-grade (G1) lesions regardless of contralateral kidney
  - preferred for larger tumours of upper ureter or kidney
  - cannot be adequately manipulated in retrograde approach due to location (lower pole calyx)
  - previous urinary diversion
  - multifocal involvement

### What techniques are available for percutaneously treating tumours of the upper tract?

- cold-cup biopsy, base cauterized: for low-grade lesions on thin stalk
- cutting loop w/ resectoscopy used to remove tumour to base: for larger broad based lesions
- tumour biopsied, laser used to treat base
  - leave NT in all cases: do 2<sup>nd</sup> look nephroscopy

### What are the results after percutaneous management of upper tract UCC?

- recurrence rates for grade 1, 2, 3: 18%, 33%, 50%
  - pts w/ grade 3 disease do poorly regardless of modality, should undergo NUU to maximize cancer therapy
  - **perc approach only for grade 1 lesions**
  - grade 2 lesions: controversial → **do not perc**

### What is the management of isolated positive upper tract cytology?

- Ix
  - urine C&S: r/o UTI
  - IVP: r/o stone
  - retrograde pyelogram
  - cystoscopy
  - biopsy bladder **and urethra**
  - ureteroscopy

## **Chapter 80 Questions - Upper tract UCC.doc**

- require frequent re-evaluation
- Treatment
  - instillation of BCG/chemo
    - stents
    - perc NT
  - NUU not recommended → do not do NUU only for +ve cytology!!!

### **What are the causes of false +ve cytology?**

- any source of inflammation
  - UTI
  - stone

### **What is the role for adjuvant topical therapy in upper tract UCC?**

- unclear role in prophylaxis
- treatment for CIS, multifocal disease

### **What are the options for adjuvant tx after nephron sparing surgery for upper tract UCC?**

- instillation therapy
- brachytherapy
  - iridium wire: can cause fistula formation

### **How can one perform instillation therapy for upper tract UCC?**

- antegrade instillation via NT
- retrograde tx: stent

### **What are the results after instillation therapy for upper tract UCC?**

- no individual study has shown statistical improvement in survival or recurrence

### **What is the most common complication of instillation tx?**

- bacterial sepsis

### **What are the results of adjuvant rads after NUU for upper tract UCC?**

- radiation does not decrease local relapse or protect against distant failure

### **How does one followup pts w/ upper tract UCC?**

- Physical, cytology, cystoscopy: q3mo x 1yr, q6mo x years 2-3, annually after
- IVP/retrograde yearly
- ipsilateral ureteroscopy (for pts undergoing renal-sparing surgery) q6mo x first few yrs, annually after
- metastatic eval (if high grade or invasive disease)
  - physical, CXR, LFTs: q3mo x 1yr, q6mo x yrs 2-3, yearly x yrs 4-5
  - CT/MR abdo/pelvis: q6mo x yrs 1-2, annually yrs 3-5
  - bone scan: only if increase ALP, bone pain

### **Why is ureteroscopy needed for followup in pts w/ upper tract UCC?**

- radiographic evaluation of upper tracts not adequate to visualize most tumour recurrences
  - 75% not seen on imaging

### **What is the treatment of metastatic UCC from the upper tract?**

- same as bladder UCC: is chemosensitive
- limited data available
- MVAC has highest response
  - toxicity is high, and dose-limiting
- newer agents: gemcitabine, paclitaxel, ifosfamide, carboplatin



## **Chapter 81**

### **• Neoplasms of the Testis •**

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#### **How can one classify germ cell tumours?**

- Precursor lesions: CIS (intratubular germ cell neoplasia)
- Tumours of one histologic type
  - seminoma (50%)
  - nonseminoma (50%)
    - embryonal carcinoma
    - yolk sac tumour
    - choriocarcinoma
    - teratoma: mature teratoma, dermoid cyst, immature teratoma, teratoma w/ malignant areas
- Mixed forms

#### **What is the WHO classification of testicular tumours?**

- Germ Cell tumours (as above)
- Sex cord / Gonadal stromal cell tumours
  - Leydig cell tumour
  - Sertoli cell tumour
  - granulosa cell tumour: adult or juvenile type
  - incompletely differentiated sex cord/gonadal stromal tumours
  - mixed forms
- Tumours of the tunica, epididymis, spermatic cord, supporting structures
  - adenomatoid
  - mesothelioma
  - adenoma
  - carcinoma
  - melanotic neuroectodermal
  - desmoplastic small round cell tumour
- Tumours containing both germ cell and sex cord/gonadal stromal elements
  - gonadoblastoma
  - mixed germ cell-sex cord/gonadal stromal tumours
- Lymphoid and hematopoietic tumours
  - lymphoma
  - plasmacytoma
  - leukemia
- Tumours of collecting ducts and rete
  - adenoma
  - carcinoma
- Miscellaneous
  - carcinoid
  - tumours of ovarian epithelial types
- Secondary tumours
- Tumour-like lesions
  - orchitis
  - malakoplakia
  - sperm granuloma
  - vasitis nodosa
  - epidermal cyst
  - cystic dysplasia

#### **What are the 3 subtypes of pure seminoma and their relative incidence?**

- classic, or typical: 82-85%



## Chapter 81 Questions - Testis Ca.docnccer

- composed of islands of large cells w/ clear cytoplasm and densely staining nuclei
- syncytiotrophoblastic elements in 10-15%
- lymphocytic infiltration in 20%
- anaplastic: 5-10% → term no longer used: defined based on # of mitotic figures / HPF
  - increased mitotic activity, nuclear pleomorphism, cellular anaplasia
- spermatocytic: 2-12%
  - cells vary in size, deeply pigmented cytoplasm and rounded nuclei containing filamentous chromatin

### What is meant by the "burnt out" testis?

- scar and intratubular calcification
- metastatic GCT and clinically normal testes
- IGCNU

### What is the age distribution of classic seminoma and anaplastic seminoma?

- Classic
  - usually occurs in men in their 30s, also in 40-50s
  - rarely if ever occurs in adolescent
  - may occur in men in their 60s
- Anaplastic: same as classic
- Spermatocytic: 50% occur in men > 50

### What histologic features exist that suggest that anaplastic seminoma is more aggressive than classic?

- greater mitotic activity
- higher rate of local invasion
- increased rate of metastatic spread
- **higher rate of tumour marker (hCG) production in anaplastic seminoma**
  - may have granulomatous inflammation in seminoma

### What are the results of treatment of anaplastic seminoma compared to classic seminoma?

- no difference when treated appropriately and compared stage-for-stage
  - less favourable results for anaplastic may reflect greater metastatic potential

### What is the prognosis of spermatocytic seminoma?

- metastatic potential is extremely low, prognosis favourable
  - no cases of mets
  - can rarely have associated sarcoma: high grade undifferentiated RMS

### What are the pathologic findings in spermatocytic seminoma?

- no relation to seminoma, not associated w/ CIS
- 3 cell types, most resemble spermatogonia
  - focal differentiation into spermatocytes
  - diploid

### Why does embryonal have the worst prognosis?

- least differentiated

### What are the histologic patterns of NSGCT?

- embryonal → highly malignant
  - distinctly malignant epithelioid cells in glands/tubules
  - pleomorphism, mitotic figures, giant cells seen, cell borders indistinct, pale cytoplasm, coarse chromatin
- choriocarcinoma
  - may present w/ **distant mets, despite small intratesticular primary**
  - when mets occur, usually chorio only: unaltered → usually vascular space invasion
  - 2 distinct and appropriately oriented cell types: syncytiotrophoblasts and cytotrophoblasts
- teratoma
  - contain more than 1 germ cell layer in various stages of maturation and differentiation
  - mature: resemble benign structures from normal ectoderm, mesoderm, and endoderm
  - immature: consist of undifferentiated primitive tissue from each of the 3 cell layers
    - PNET: primitive neuroectodermal tumour
  - malignant degeneration may occur in differentiated tissues → *malignant teratoma*

## Chapter 81 Questions - Testis Cancer

- yolk sac
  - epithelioid cells that form glandular and ductal structures arranged in columns, papillary projections, or solid islands
  - commonly seen embryoid bodies, hyaline globules, Schiller-Duval body (rare)
  - most common patterns: microcystic/reticular, glandular
- mixed: 60% of all GCTs

### What must be demonstrated histologically to diagnose choriocarcinoma?

- 2 distinct and appropriately oriented cell types:
  - syncytiotrophoblasts: large multinucleated cells, large amount of vacuolated eosinophilic cytoplasm
  - cytotrophoblasts: closely packed intermediate sized cells w/ distinct cell border, clear cytoplasm, single nucleus

### What is the most common testis tumour of infants and children?

- yolk sac (not true as per – J Urol Dec 2003 lists mature teratoma as most common nowadays)
  - mature teratoma (43%), RMS (26%), epidermoid cyst (10%), yolk sac (8%) and germ cell tumors (6%)

### What tumour is responsible for the production of AFP?

- yolk sac

### What are embryoid bodies?

- aka polyembryoma
- ovoid structures measuring 1-2mm in diameter, consisting of a cavity surrounded by loose mesenchyme w/ cyto- and syncytiotrophoblasts
- common finding in yolk sac tumours: resemble 1-2 week old embryos

### What are the histologic differences b/w mature and immature teratoma?

- mature elements resemble benign structures derived from normal ectoderm, endoderm, and mesoderm
- immature teratomas consist of undifferentiated primitive tissues from each of the 3 germ cell layers

### What is the most common combination of histologic pattern seen in mixed NSGCT?

- embryonal, yolk sac, teratoma, and syncytiotrophoblasts
  - in 60% of testis tumours, > 1 histologic pattern identified

### What histologic pattern is most commonly seen in mets associated w/ teratomas?

- usually contain embryonal (80%); less frequently teratoma or choriocarcinoma

### What percentage of pts dying w/ seminoma contain nonseminomatous mets?

- 30-45%
- converse is rarely seen

### Which one subtype of germ cell tumour does not have testicular CIS as a preinvasive precursor?

- spermatocytic seminoma

### What is the natural history of testicular CIS?

- 50% of men w/ CIS on bx develop invasive disease w/i 5 yrs if left untreated
  - "invasive" = invasion through the BM
- incidence of CIS in male population: 0.8%

### What is the origin of testicular CIS?

- originates from fetal gonocytes
  - characterized by seminiferous tubules containing only Sertoli cells and malignant germ cells in single row
  - seminoma-like cells scattered along BM
  - easiest to find adjacent to GCT
  - confirm w/ +ve stain for PLAP

### What is the risk of developing a GCT in the contralateral testis in pts w/ testis cancer?

- 5.2%, similar to the prevalence of CIS in the contralateral testis

### Should one biopsy the contralateral testis in pts w/ testicular CIS?

- No
  - prolonged course of CIS, s/e of therapy, second primary GCTs respond to tx

## Chapter 81 Questions - Testis Ca.docnccer

→ may be reasonable to biopsy and treat pts w/ high risk: infertility, cryptorchidism, atrophic testis, EGCT, intersex

### What are the RF for the development of testicular CIS?

- hx of testicular carcinoma
- EGCT: 40%
- cryptorchidism
- contralateral testis w/ unilateral testis cancer: 5-6%
- atrophic contralateral testis w/ unilateral testis cancer: 30%
- somatosexual ambiguity: 25-100%
- infertility

### What is the intratesticular distribution of CIS?

- usually evenly distributed throughout the testis

### How does one diagnose testicular CIS?

- biopsy only
  - there is no established tumour marker for CIS

### What are the treatment options for CIS?

- observation
- radiation therapy
- chemotherapy
- orchiectomy

### When are the peak incidences of each subtype of testicular cancer?

- overall: infancy (0-10), early adulthood (20-40), late adulthood (>60)
- yolk sac: <10
- pure teratoma: <10
- choriocarcinoma: 20-30 (1%)
- embryonal: 30-40 (3-4% in pure form)
- teratocarcinoma: 30-40 (5-10%)
- seminoma: 35-39 (30-60%)
  - rare before age 10 and after age 60
  - most common type overall
- spermatocytic seminoma: >50
- malignant testicular lymphoma: >50

### What factors exist that affect incidence of testis cancer?

- Race
  - testis ca in American blacks is 1/3 that of American **whites**, but 10X that of African blacks
  - **Jewish** people have an 8X higher incidence
- Genetics
  - no higher incidence in twins
- Laterality
  - more common on R side
  - 2-3% bilateral: **seminoma most common**

### What are the possible etiologies of testis cancer?

- Congenital
  - cryptorchidism: 3-14X relative risk
    - 5-10% pts w/ testis cancer develop testis ca in contralateral descended testis (similar to 5.2% risk of contralateral CIS)
- Acquired
  - trauma: no evidence
  - hormones: estrogen or DES during pregnancy
    - estrogen during pregnancy may cause Leydig cell tumours
  - atrophy: nonspecific or mumps-associated atrophy - speculative

### What are the RF for development of testis cancer?

- race (Whites 1 in 500 lifetime risk, less in Blacks and Asians)
- geography (highest in Scandinavia)

## Chapter 81 Questions - Testis Ca.docnccer

- cryptorchidism
- family history (brother = 10x RR)
- hormonal exposure (in utero DES)
- CIS (intra-tubular germ cell neoplasia: 50% progress in 5yrs)
- contralateral testis cancer
- testicular microlithiasis

### What is the significance of testicular microlithiasis?

- DDx: CIS/GCT, infection, infertility, UDT, testicular atrophy, varicocele, torsion
  - infertility: uncertain relationship
  - malignancy: TM in 50-75%, usually in NSGCT → **significant association w/ CIS**
- incidence of 0.6%: more frequent in UDT
- classic description: bilateral evenly distributed bright echoes
  - classic TM: 5 or more microliths on any view
  - limited TM: < 5 microliths
- usually asymptomatic: may have orchalgia
- Management
  - all pts get physical exam, markers, repeat US
  - US, markers, PE early if no change in 5 years, self-exam
  - biopsy testicle if:
    - focal, clumped and unilateral w/o mass
    - TM in infertile men, UDT, or atrophic testis
    - ipsilateral testis ca and TM in contralateral testis
  - no role for bx if classic TM: bilateral and evenly distributed

### What factors may play a causative role in the development of testis cancer in patients w/ cryptorchidism?

- abnormal germ cell morphology
- elevated temperature
- interference w/ blood supply
- endocrine dysfunction
- gonadal dysgenesis

### Describe the natural history of germ cell tumours.

- 50% of pts w/ NSGCT present w/ disseminated mets
- complete regressions are rare
- all germinal tumours in adults = malignant
- local involvement of epididymis or cord occurs in 10-15%, increasing risk of hematogenous mets
- lymphatic mets occur in all forms except choriocarcinoma (which disseminates hematogenously)

### Describe the pattern of spread of germ cell tumours.

- predictable and stepwise fashion, **except for choriocarcinoma**
- primary drainage of R testis: interaortocaval nodes
- primary drainage of L testis: paraaortic nodes, bounded by L ureter, L renal vein, aorta, and origin of IMA
- lymphatic drainage X over from R to L
- suprahilar LN spread rare in N1 disease, but not uncommon in N2 disease
- lymphatics of epididymis drain into external iliac chain
- inguinal node mets can occur from scrotal involvement, previous OR, or retrograde lymphatic spread from massive retroperitoneal LN deposits
- testicular lymphatics can occasionally bypass the retroperitoneal nodes and communicate directly w/ thoracic duct
  - associated w/ 5% distant failure rate

### What is the doubling time of GCT?

- 10-30 days

### What % of patients fail after orchiectomy alone for stage A testis cancer?

- NSGCT
  - 30% fail w/ surveillance only: 80% w/ retroperitoneal LN, 20% w/ distant mets
  - 5-10% relapse after RPLND
- Seminoma
  - 17% fail w/ surveillance only, at mean of 15months

## Chapter 81 Questions - Testis Ca.docncer

### What are the presenting symptoms in a pt w/ testis cancer?

- nodule or painless swelling of one gonad: noted by patient or partner
- dull ache or heavy sensation
- acute pain in 10%
- infertility
- associated epididymitis or bleeding into the tumour
- gynecomastia in 5%, due to increased hCG, somatomammotropin, PRL, estrogens, or androgens
- sx due to mets: 10%
  - neck mass
  - cough or dyspnea
  - GI disturbances
  - lumbar back pain
  - bone pain
  - CNS manifestations
  - lower-extremity swelling

### What is important in the physical exam?

- examination of the scrotal contents
  - size, contour, consistency, mass
- palpation of abdomen: ?nodal disease
- supraclavicular LN
- chest: gynecomastia or lung involvement

### How does one stage testis cancer?

- Testicular Cancer Staging System of the American Joint Committee on Cancer and the International Union Against Cancer (AJCC and IUAC)
- Primary Tumour
  - pTX: primary cannot be assessed
  - pT0: no evidence of primary tumour in testis
  - pTis: CIS
  - pT1: tumour limited to testis/epididymis, no vascular/lymphatic invasion
  - pT2: limited to testis/epididymis + vascular/lymphatic invasion, or tumour involvement of tunica **albuginea & vaginalis**
  - pT3: invades spermatic **cord**
  - pT4: invades **scrotum**
- Nodes
  - Clinical
    - NX: regional LN cannot be assessed
    - N0: no evidence of LN mets
    - N1: LN mass < 2cm
    - N2: one or many LN masses 2-5cm
    - N3: LN mass > 5cm in greatest dimension
  - Pathologic
    - pN0: no tumour in LN
    - pN1: LN mass <2cm and ≤5 nodes +ve
    - pN2: LN mass 2-5cm, >5 LN + (all < 5cm), evidence of extranodal extension of tumour
    - pN3: LN mass >5cm
- Mets
  - M0: no mets
  - M1: nonregional nodal or lung mets
  - M2: nonpulm visceral mets
- Serum Markers
  - S0: LDH ≤ N, hCG ≤ N, AFP ≤ N
  - S1: LDH <1.5 x N, hCG < 5000, AFP < 1000
  - S2: LDH 1.5-10 x N, hCG 5000-50000, AFP 1000-10000
  - S3: LDH > 10 x N, hCG > 50000, AFP > 10000
- Royal Marsden Staging System
  - Stage I: disease confined to tests
    - Stage IM: rising markers post orchidectomy
  - Stage II: abdominal lymphadenopathy

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- IIA: nodes < 2cm
- IIB: nodes 2-5cm
- IIC: nodes > 5cm
- Stage III: supra-diaphragmatic disease
  - IIIA: nodes < 2cm
  - IIIB: nodes 2-5cm
  - IIIC: nodes > 5cm
- Stage IV: extra-lymphatic mets
- Stage L: lung mets
  - L1: < 3 lung mets
  - L2: > 3 lung mets
  - L3: > 3 lung mets, 1 or more > 2cm
- Stage H+: liver involvement

### What is the chance of a false-negative clinical staging error in testis cancer?

- overall stage T1-T3N0M0 false –ve rate 20%
  - 10-15% of pts w/ clinical stage 1 that undergo RPLND have undetected nodal mets
  - another 5-10% relapse after surgery, usually extranodal sites

### What is the stage grouping for testis cancer according to the AJCC staging system?

- Stage 0: **pTis** N0 M0 S0
- Stage I: T1-4 **N0 M0 SX**
  - Stage Ia: **T1** N0 M0 S0
  - Stage Ib: **T2-4** N0 M0 S0
  - Stage Is: any T N0 M0 **S1-3**
- Stage II: any T **any N M0 SX**
  - Stage IIa: any T **N1** M0 S0-1
  - Stage IIb: any T **N2** M0 S0-1
  - Stage IIc: any T **N3** M0 S0-1
- Stage III: any T any N **M1 SX** or any T any N M0 **S2-3**
  - Stage IIIa: any T any N M1 S0-1
  - Stage IIIb: any T any N M0-1 S2
  - Stage IIIc: any T any N M0-1 S3

### What is the first radiologic study to be performed in staging?

- CXR

### What is the role of chest CT in staging testis ca?

- CT chest can find lesions as small as 2mm in size
  - 70% of these are benign processes
- should be used in pts w/ abnormal abdominal CT

### What are the characteristics of testis ca on MRI?

- tumours are hypointense on T2-weighted images
- brisk and early enhancement after IV gadolinium
  - ?no advantage over CT in imaging and staging

### How can one classify tumour markers for testis ca?

- oncofetal substances associated w/ embryonal development: **either AFP or hCG or both elevated in 90% of NSGCT**
  - AFP (alpha fetoprotein)
    - elevated in 50-70% of NSGCT
  - hCG (human chorionic gonadotropin)
    - elevated in 40-60% of NSGCT
- cellular enzymes
  - LDH (lactic acid dehydrogenase)
    - high levels in muscle (all types), liver, kidney, brain
    - low specificity to testis cancer
    - direct relx b/w LDH and tumour burden
    - may be only elevated marker in up to 10% of pts w/ persistent/recurrent NSGCT
  - PLAP (placental alkaline phosphatase)

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- different than adult ALP
- 40% of pts w/ advanced disease have elevated PLAP
- GGTP (gamma-glutamyl-transpeptidase)
  - hepatocellular enzyme elevated in liver disease
  - increased in 1/3 pts w/ seminoma

### Which cells produce AFP and hCG?

- **AFP produced by fetal yolk sac**, liver and GI tract
  - produced by epithelial lining of cysts and tubules in yolk sac tumours
  - highest concentrations noted during 12<sup>th</sup> to 14<sup>th</sup> week of gestation, decline up to 1 yr of life
- **hCG produced by syncytiotrophoblasts** in placenta during pregnancy for maintenance of the corpus luteum
  - alpha and beta polypeptide chains: alpha chain similar to other pituitary hormones LH, FSH, TSH)

### What is the T<sub>1/2</sub> of AFP and hCG?

- AFP: 5-7days
  - should be undetectable by 1 yr of life (<40 ng/mL)
- hCG: 24-36 hours
- markers that decline according to T<sub>1/2</sub> more likely to remain disease free
  - **but, normalization of markers after tx does not mean pt is disease free**

### Which tumour subtypes are associated w/ AFP and hCG?

- AFP may be produced by pure embryonal, teratocarcinoma, yolk sac, or mixed: elevated in 50-70%
  - **is not produced by pure choriocarcinoma or pure seminoma**
  - detection of elevated AFP strongly suggests NSGCT
- hCG produced by all pts w/ choriocarcinoma and 40-60% of pts w/ embryonal
  - 5-10% of seminomas have elevated hCG due to syncytiotrophoblastic elements: may be as high as 500
  - if hCG normalizes after orchiectomy, pts should be treated as having pure seminoma

### What is the DDx of an elevated AFP or hCG?

- AFP
  - malignancy: testis, liver, pancreas, stomach
  - normal pregnancy
  - benign liver disease: drugs (chemo, anaesthetics, antiepileptics), viral hepatitis, EtOH abuse
  - ataxia telangectasia
  - tyrosinemia
- hCG
  - pregnancy
  - malignancy: GCT, liver, pancreas, stomach, lung, breast, kidney, bladder
  - marijuana smokers
  - hypogonadism: false +ve in pts w/ elevated LH (cross-reactivity w/ alpha subunit)

### What are the most important prognostic factors for determining survival in pts w/ GCTs?

- elevation of tumour markers
  - persistently elevated markers after orchiectomy = systemic mets → for chemo
- number of metastatic sites
- bulk of disease

### What is the treatment of the "violated" scrotum or tumour spillage?

- surgical excision of the retained spermatic cord remnant or of the contaminated scrotum
  - irradiation of groin and ipsilateral hemiscrotum alone if pure seminoma
- Jewett: treatment of the clinically normal "violated" scrotum is not necessary unless clinical recurrence

### What is the difference in tumour stage at presentation in seminomas vs. NSGCTs?

- seminomas: 65-85% clinically confined to testis
  - 10-15% have retroperitoneal mets
  - < 5-10% have juxtaregional LN or visceral mets
- NSGCTs: 60-70% present w/ recognizable mets

### Describe the treatment algorithm used for seminoma after orchiectomy.

- Stage I seminoma

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- stage Is (persistent tumour markers, radiologic studies –ve): chemotherapy (type: ?EP or carboplatin)
- spermatocytic: no adjuvant tx
- typical and anaplastic
  - no RF (>6cm primary, vasc/lymphatic invasion, normal hCG): **surveillance** if motivated and reliable
  - RF present: **low dose abdo/pelvic radiation (para-aortic nodes only) 25 Gy**
    - ◆ chemo: MRC phase III trial comparing carboplatin vs. rads in stage I seminoma
- Stage IIa and IIb
  - **abdo/pelvic radiation (ipsilateral external iliac, bilateral common iliac, paracaval, para-aortic including cisterna)**
    - may increase field if violated scrotum or retained cord remnant
    - 25-35 Gy: fractionated doses of 150 cGy/day, 5d per week
  - chemo if LN close to kidney: irradiation of kidney avoided due to sensitivity of renal parenchyma to rads
- Stage IIc and Stage III
  - platinum based **chemo (EP)**, no further treatment if CR
  - if residual mass post-chemo:
    - diffuse desmoplastic reaction: observation
    - discrete well delineated mass > 3cm: resection (viable tumour in 30% - MSK review)
      - ◆ Indiana group: follows pts w/ CT q3mo x 1 year, q4mo x 1 year → only operates on masses that grow
    - ◆ mass necrosis/fibrosis: observation
    - ◆ residual GCT: salvage chemo – VIP

### What are the contraindications for surveillance in pts w/ NSGCT?

- high risk for recurrence: T2 disease, lymphovascular invasion, lack of yolk sac elements, high % of embryonal (>40%)
- greater than stage I disease
- unreliable or unmotivated pt
- pt anxious about surveillance, or requests surgical therapy
- cognitive impairment: not able to understand risks/benefits of surveillance

### Where are the usual sites of mets in pts that die w/ seminoma?

- liver and lung involvement: 75%
- bone: 50%
- brain: 25%

### What are the chances of relapse post-orchietomy for surveillance w/ stage I seminoma?

- without radiation therapy, 17% of pts relapse w/ median time of 15 months
  - OS 98%
- nationwide Danish study w/ 261 pts (von der Maase, 1993) → 4 yr relapse-free survival rate (?typo):
  - size < 3cm: 6%
  - 3-6cm: 18%
  - > 6cm: 36%

### How much radiation is typically administered for low-stage seminoma?

- 25Gy to paraaortic nodes only

### What are the 5-yr survival stats of seminoma?

- Stage I: survival of >95% in numerous studies
- Stage II: 70-92%, average 80% if tx w/ rads
  - stage IIa: >90%, similar to stage I
  - **stage IIc tx w/ rads alone: half develop mets outside radiated fields and need chemo**
- Stage III: >90% CR to chemo alone
  - > 90% of responders NED at 4yrs

### What LN groups are included in radiation tx fields for stage II seminoma?

- ipsilateral external iliac
- bilateral common iliac
- paracaval
- para-aortic nodes superiorly, including cisterna chyli
  - contralateral para-aortic nodes treated on individual basis
- avoid irradiation of kidney!

### How are the radiation fields modified in a patient w/ previous hernia repair or orchiopexy?



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- alteration in lymphatic drainage, so inferior portion of field includes contralateral inguinal region as well
- contralateral testis is shielded

### What are the chances of relapse after radiation in pts w/ stage II seminoma?

- Royal Marsden Hospital (Peckham, 1981)
  - N1: 10%
  - N2: 18%
  - N3: 38%

### How does previous radiation affect results in a patient receiving chemo for seminoma?

- RR higher in patients receiving cisplatin-based chemo as primary tx if no previous rads
- RR higher in patients receiving chemo vs. rads alone

### What is the management of a retroperitoneal mass post-chemo for seminoma and why?

- seminoma involves the retroperitoneum as a diffuse fibrotic process
  - residual necrosis/fibrosis usually found
  - clean retroperitoneal dissection rarely achieved
  - increased morbidity in resection of post-chemo mass w/ seminomatous elements (Donohue, 2003)
- surgery only justifiable if residual disease well delineated and distinct from surrounding structures
  - MSK review (Herr 1997): viable tumour in 30% if residual mass > 3cm
  - may decrease w/ time → unclear if resection or further tx needed
- Indiana group: follow pts w/ serial CTs
  - Indiana indications for resection: increased mass size on serial imaging, increasing markers, clinical progression, or proven GCT on biopsy

### What is the follow-up for the patients w/ a residual mass post-chemo?

- CT: q3mo x 1 yr, q4mo x 2<sup>nd</sup> yr, q6-12mo x 3<sup>rd</sup>-5<sup>th</sup> yrs

### What is the surveillance schedule needed for seminoma post-orchietomy?

- markers q4mo x 3 yrs
- abdo/pelvis CT q4mo x 3 yrs, then q6mo x 4 yrs, then yearly until yr 16
- CXR q8mo x 2yrs, then yearly until yr 16

### Why is RPLND post-orchietomy usually necessary for stage T1-3 N0 M0 NSGCT?

- 20-25% of pts w/ low-stage NSGCT understaged by all non-surgical modalities

### What is the cure rate for stage I NSGCT w/ surgery (RPLND) alone?

- 95%
- so, 5% relapse post-RPLND: high cure rate w/ chemo

### Describe the treatment algorithm for NSGCT post-orchietomy.

- Low-stage disease
  - Stage I
    - no RF (T2 or higher, embryonal > 40%, vascular/lymphatic invasion, no yolk sac): **surveillance** if motivated, reliable
      - ◆ otherwise: RPLND or primary chemo
    - RF present: **modified RPLND** or **chemotherapy** (3 cycles BEP)
      - ◆ stage N0-1: observation
      - ◆ stage N2: adjuvant chemo (2 cycles BEP)
    - stage IS: chemotherapy (3 cycles BEP)
  - Stage IIa or IIb
    - bilateral RPLND or chemotherapy (3 cycles BEP)
      - ◆ stage N0-1: observation
      - ◆ stage N2: adjuvant chemotherapy (2 cycles BEP)
- High-stage disease (stage IIc or stage III)
  - good risk disease: chemotherapy (3 cycles BEP)
    - resolution of disease: observation
      - ◆ recurrence: salvage chemo +/- high-dose chemo + ABMT or stem cell transfer
        - ◆ if CR: observation
        - ◆ poor response or elevated markers: "desperation surgery" (excise all residual disease)
        - ◆ if late relapse (> 2 yrs): 2<sup>nd</sup> line chemo

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- residual retroperitoneal mass: bilateral RPLND
  - ◆ if necrosis, fibrosis, teratoma: observation
  - ◆ residual GCT: salvage chemo (VIP)
- residual visceral/brain mets: resection
- persistent tumour markers: salvage chemo (VIP)
  - ◆ must exclude false +ve hCG or AFP
  - ◆ exclude sanctuary site (brain mets, contralateral testis)
- **poor risk disease: mediastinal primary, nonpulmonary visceral mets, or S3 markers**
  - chemotherapy (ifosfamide substitutes, etoposide, high dose chemo + ABMT or stem cell transfer)
    - ◆ poor response to chemo, elevated markers: salvage chemo
    - ◆ inadequate response: "desperation surgery"

### What is the role of radiation in low-stage NSGCT?

- accepted practice outside N.America
- has been shown to decrease risk of relapse (from 27% to 16%) w/ observation in clinical stage I disease
  - relapse after rads for clinical stage I NSGCT has been shown to be as high as 24%

### What are the disadvantages in using radiation for stage I NSGCT?

- inaccuracy in staging retroperitoneal LN
- lack of survival data that can be compared w/ surgical data
- if relapse post-rads, prior radiation may prevent adequate chemo or surgical excision

### What is the tumoricidal dose for NSGCT?

- 50 Gy

### What are the long-term complications of para-aortic radiation?

- radiation enteritis, bowel obstruction, BM suppression: 5-10%
- 2<sup>nd</sup> malignancy: 18% at 25 years
  - stomach, bladder, possibly pancreas

### What is the follow-up for low-stage NSGCT?

- Hx/Px, markers, CBC, LFT: q1mo x 1 yr, q2mo x 2<sup>nd</sup> yr, q4mo x 3<sup>rd</sup> + 4<sup>th</sup> yr, q6mo x 5<sup>th</sup> yr
- CXR: q1mo x 1yr, q2mo x 2<sup>nd</sup> yr, q3-4mo x 3<sup>rd</sup> + 4<sup>th</sup> yr, annually after
- CT abdo: q2-4mo x 2 yrs, q6mo x 3<sup>rd</sup> + 4<sup>th</sup> yr, annually after
- surveillance for minimum 5-10 years post-orchietomy

### What is the relapse and death rate for surveillance only (no RPLND) after low-stage NSGCT?

- 28% relapse, 54% within the retroperitoneum: should represent the % of pts understaged by imaging alone (20-25%)
  - of the pts that relapse, 7% die of their disease

### What is the definition of non-compliance in surveillance protocols, and how often does it occur?

- missing more than 1 CT
- missing more than 2 consecutive clinic visits, markers, or CXRs
- compliance 61% in 1<sup>st</sup> year, only 35% in 2<sup>nd</sup> year
  - especially poor w/ CT scans

### What are the factors that predict +ve LN after orchietomy and relapse after orchietomy and RPLND?

- vascular or lymphatic invasion: most important
- T stage of primary tumour (T2 or above): invasion of epididymis or tunica albuginea
- presence of embryonal carcinoma (>40%)
- lack of yolk sac elements
- ?lack of teratoma in primary
- ?increased markers preop

### What are the results and the advantages of primary chemotherapy in low-stage NSGCT?

- overall 5-yr survival in pts that get 2 cycles BEP or PVB for stage I NSGCT > 95%
- advantage of treating mets outside retroperitoneum (that RPLND fails to get)
  - will hit the 5-10% that fail post-RPLND
- low relapse rates (0-16%), less intensive follow-up

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### What should be performed if suspicious LN are found at RPLND?

- complete bilateral RPLND

### What is the role of adjuvant chemo after RPLND in stage II disease?

- controversial whether adjuvant chemo needed for pts w/ +ve LN that has been completely resected
  - 48% relapse if observation after RPLND (no difference if N1, N2 or N3) vs. 2% if 2 cycles adjuvant PVB or AVBC
- can observe if minimal nodal disease resected completely w/ careful F/U

### What is the role of primary chemo in stage IIb disease?

- chemo favoured as primary treatment in pts w/ LN > 3cm
  - controversial re: primary chemo vs. RPLND in IIa/IIb disease → appear to be equivalent
  - 23% of pts w/ clinical IIa/IIb actually have pathologic stage I, 65% cured w/ RPLND alone

### What is the role for radiation in stage IIa/IIb disease?

- fallen into disuse
  - disease often coexists outside peritoneum
  - supplementary rads to large nodal deposits in stage III disease

### How are pts stratified into risk classifications for testicular cancer?

- International Germ Cell Consensus Classification (1997)
- Good Prognosis
  - NSGCT
    - testis or retroperitoneal primary
    - no non-pulm visceral mets
    - S1 markers: AFP < 1000, hCG < 5000, and LDH < 1.5 x N
  - Seminoma
    - any primary
    - no non-pulm visceral mets
    - normal AFP, any hCG or LDH
- Intermediate Prognosis
  - NSGCT
    - testis or retroperitoneal primary
    - no non-pulm visceral mets
    - **S2 markers:** any of AFP 1000-10000, hCG 5000-50000, or LDH 1.5-10 x N
  - Seminoma
    - testis or retroperitoneal primary
    - normal AFP, any hCG or LDH
    - **nonpulmonary visceral mets**
- Poor Prognosis
  - NSGCT only
    - **mediastinal** primary
    - **nonpulmonary visceral mets**
    - **S3 markers:** AFP > 10000, hCG > 50000, or LDH > 10 x N

### How does good-risk vs. poor-risk disease modify treatment?

- good risk: standard chemo (BEP) w/ 91-95% RR
  - same results w/ 3 vs. 4 cycles of chemo
  - poor results when carboplatin substituted for cisplatin, or if bleo deleted
- poor risk: need more aggressive chemo, since only 53% RR w/ standard chemo

### What is the high-dose chemo regimen for poor-risk disease?

- 4 cycles BEP

### Stage by stage, what are the pros and cons of each treatment option?

| Stage        | Pros  | Cons   |
|--------------|---|--|
| I            |   |  |
| Surveillance | Avoid morbidity of RPLND<br>Majority (~75%) true stage I (node -) –<br>avoid unnecessary RPLND<br>Survival not impaired if followed closely | ~25% radiologically downstaged (nodes truly +)<br>If lost to follow-up or poor compliance,<br>then a problem |

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|   |  |  |
|---|--|--|
|   | and salvage RPLND or chemo used promptly   | No definitive surgical staging<br>Mortality in some series ~7%   |
|   | 5-10% <sup>^</sup> of relapses outside RP, so need Rx beyond RPLND anyways   |  |
|   | ? cheaper  |  |
| Primary RPLND                                 | Get definitive staging information<br>25% radiologically downstaged (cured by RPLND)<br>Chance of subsequent RP recurrence essentially 0 | Morbidity of RPLND<br>Emission failure   |
|   | Get definitive surgical staging<br>May save 2 courses of chemo   |  |
| Primary XRT                                   | Not used in N.A.   | Staging inaccuracy<br>Chemo and RPLND more difficult post-XRT  |
| Primary chemotherapy                          | May avoid RPLND<br>High rate of cure<br>No impaired mortality<br>Maintain emission   | Morbidity of BEP<br>75% who are truly node negative receive unnecessary chemo<br>No definitive surgical staging  |
| Ila and Iib                                   |  |  |
| Chemotherapy (BEP) +/- salvage RPLND          | If nodes completely regress may avoid RPLND<br>Makes RPLND easier<br>Higher chance of nerve sparing if tumour bulk minimized pre-op      | Side effects of chemo (2 cycles).<br>Radiologic understaging.  |
| Primary RPLND +/- adjuvant chemo              | May avoid 2 cycles of BEP<br>Lower post-op morbidity before belomycin given  | May be radiologically understaged (i.e. open and find large masses, more technically difficult)<br>High risk of emission failure if large masses found at time of OR |
| Iic   |  |  |
| Chemotherapy then RPLND PRN                   | Makes RPLND easier<br>May avoid RPLND  | Side effects of chemotherapy.  |
| Primary RPLND +/- adjuvant chemo              | May avoid 2 cycles of BEP.   | Large masses more difficult technically.<br>High risk of emission failure.   |
| III   |  |  |
| Chemotherapy then surgery for residual masses |  |  |

### What is the management of the post-chemo mass for NSGCT?

- recurrent mass: salvage chemo
- residual mass: RPLND (including full bilateral node dissection)
  - patient selection important: if no teratoma in primary, and 90% reduction in retroperitoneal LN size seen, no GCT seen
  - if teratoma or fibrosis/necrosis, observe
  - if residual GCT, require additional chemo

### What factors predict findings in the retroperitoneum post-chemo?

- prediction of fibrosis in retroperitoneum post chemo (74-90%)
  - no teratoma in primary
  - > 90% decrease in volume of retroperitoneal disease seen on serial CTs
  - residual mass < 1.5cm
  - elevated pre-chemo markers
- prediction of necrosis/fibrosis in retroperitoneum
  - -ve frozen section at RPLND
- prediction of necrosis/fibrosis in concomitant lung disease
  - necrosis/fibrosis in retroperitoneum → may be used to avoid lung exploration in some pts: **controversial**

### What is the only contraindication to RPLND after chemo?

- elevated tumour markers

### What histopathologic subsets of patients are seen after RPLND post-chemo?

- 40% necrosis/fibrosis
- 40% teratoma
- 20% viable GCT → need more chemo

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### What is the natural hx of residual teratoma post-chemo?

- growing teratoma syndrome: may compromise vital organ function
- malignant transformation of mature teratoma to sarcoma and adenocarcinoma: in 6-8%
  - most common histologic subtypes: RMS and carcinoma
  - resistant to chemotherapy
- teratoma may result in late recurrence
- risk of recurrent GCT
- chemo/rads ineffective against teratoma

### What medication is always used in conjunction w/ ifosfamide?

- mesna, to prevent hemorrhagic cystitis

### What is used for 2<sup>nd</sup> line chemo?

- VIP
  - do not use cisplatin if progressing after cisplatin therapy → change to carboplatin

### What is used for 3<sup>rd</sup> line chemo?

- ABMT or stem cell support w/ high-dose chemo
- carboplatin used instead of cisplatin

### What is the histologic distribution of residual masses after salvage chemo?

- 50% viable GCT
- 40% teratoma
- 10% necrosis/fibrosis

### In descending order of frequency, what are the most common sites of origin for extragonadal germ cell tumours (EGCTs)?

- mediastinum
- retroperitoneum
- sacrococcygeal region
- pineal gland

### What are the potential origins of EGCT?

- displacement of primitive germ cells during early embryonic migration from the yolk sac endoderm
- persistence of pluripotential cells in sequestered primitive rests during early somatic development
  - 3-5% of all GCTs are of extragonadal origin

### How do EGCT usually present?

- M > F
- usually present w/ advanced local disease and distant mets
- pure seminoma in 50%

### Where do EGCT spread to?

- LN, lung, liver, bone

### What are the presenting sx of primary retroperitoneal tumours?

- may reach large size w/o sx
  - abdo or back pain
  - palpable mass
  - vascular obstruction
  - constitutional sx

### What are the presenting sx of sacrococcygeal tumours?

- palpable mass
- skin discolouration or hairy nevus
- bowel or urinary obstruction

### What are the presenting sx of pineal gland EGCT?

- increased ICP: headache, visual impairment
- oculomotor dysfunction: diplopia, ptosis

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- hearing loss
- hypopituitarism: abnormal menses
- hypothalamic disturbances: diabetes insipidus

### What is the treatment of EGCT?

- excision usually not possible: frequent local extension and high rates of mets
- primary retroperitoneal seminomatous EGCT: intensive chemo
- NS EGCT: do poorly despite surgery, rads, chemo
- wide local excision for sacrococcygeal tumours, since most are benign

### What is the most common sex cord / gonadal stromal cell tumour?

- interstitial cell (Leydig's cell) tumours
  - 1-3% of all testis cancers
  - etiology unknown, no association w/ cryptorchidism
  - 10% malignant

### What histologic finding is characteristic of Leydig cell tumours?

- Reinke's crystals
  - represent crystallized testosterone
- small yellow/brown lesions
- uniform, polyhedral closely packed cells w/ round eccentric nuclei and lipoid vacuoles

### What features suggest malignancy in Leydig cell tumours?

- no reliable criteria
  - large size
  - necrosis
  - evidence of infiltration
  - vascular invasion
  - ++ mitotic activity
  - **mets: only reliable criterion of malignancy**

### How do Leydig's cells tumours present?

- prepubertal: average age 5 yrs
  - isosexual precocity: enlarged genitalia, lower voice, pubic hair
  - elevated T levels, urinary 17-ketosteroid
- adults
  - **palpable testis mass: most common presenting sx**
  - impotence, gynecomastia, decreased libido

### What is in the DDx of Leydig's cell tumour?

- feminizing adrenocortical d/o, Klinefelters, other feminizing testicular d/o

### What is the treatment and management of Leydig's cell tumours?

- radical inguinal orchiectomy
- endocrinologic studies: T, 17-ketosteroids, cortisol, dexamethasone suppression test
- CT retroperitoneum
- RPLND if malignant
- chemo: ortho-para-DDD, cisplatin, vinblastine, vincristine, bleo, cyclophosphamide, doxorubicin → limited experience

### What is the prognosis of Leydig's cell tumour?

- good: generally benign
- persistent virilizing and feminizing characteristics: some may be irreversible
- if mets, average survival 3 yrs

### What are the essential diagnostic elements of Sertoli cells tumours?

- epithelial elements resembling Sertoli cells
- varying amounts of stroma

### What are the presenting sx of Sertoli cell tumours?

- testicular mass +/- pain +/- gynecomastia

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### What is the treatment of Sertoli cell tumours?

- radical orchiectomy: curative in 90%
- RPLND if malignant
- CXR and bone scan to r/o mets
- rads/chemo: uncertain value

### What pts are at risk of developing gonadoblastoma?

- pts w/ gonadal dysgenesis

### What are the 3 elements seen histologically in gonadoblastoma?

- Sertoli cells
- interstitial tissue
- germ cells

### What are Call-Exner bodies?

- characteristic inclusions in tubules in gonadoblastoma, consisting of PAS +ve secretory material similar to that seen in BM of the tubules

### What are the clinical manifestations of gonadoblastoma?

- due to 3 factors:
  - abnormalities of external genitalia and gonads seen w/ **gonadal dysgenesis**
  - presence of germ cells w/ malignant potential
  - endocrine function of gonadal stromal tissue: androgen production
- 4/5 are phenotypic females
  - present w/ primary amenorrhea + lower abdo mass
- phenotypic males
  - cryptorchidism, hypospadias, some female internal genitalia
  - may have gynecomastia

### What is the treatment of gonadoblastoma?

- radical orchiectomy
  - **bilateral if gonadal dysgenesis present**
- all streak gonads in patients w/ gonadal dysgenesis should be removed

### What is the prognosis of adenocarcinoma of the rete testis?

- highly malignant
  - 50% die w/i 1 year
  - mets to inguinal and retroperitoneal LN, lungs, bone, liver
- chemo/rads have little benefit

### What is the origin of adrenal rest tumours?

- arise from adrenocortical rests that occur normally in the testis
- dependent on ACTH for growth and steroid secretion
- bilateral testis tumours associated w/ CAH

### What is the most common secondary neoplasm of the testis?

- lymphoma
  - most frequent of all testis tumours in patients older than 50

### What is the typical histologic appearance of lymphoma?

- diffuse replacement of the normal architecture, w/ focal sparing of the seminiferous tubules
- testis diffusely enlarged to 4-5cm

### What is the common clinical presentation of testicular lymphoma?

- painless enlargement of testis
- generalized constitutional sx: wt loss, weakness, anorexia
- bilateral tumours in 50%

### What investigations are needed for testicular lymphoma?

## **Chapter 81 Questions - Testis Ca.docnccer**

- CBC and smear, bone marrow, CXR, bone scan, CT, lymphogram, liver and spleen scan

### **What is the treatment of testicular leukemia?**

- rads w/ 20Gy in 10 fractions
- orchiectomy probably unwarranted  
→ biopsy required for diagnosis

### **In order of frequency, what are the most common primary sources of mets to testis?**

- prostate, lung, GI tract, melanoma, kidney

### **What are the most common tumours of the paratesticular tissues?**

- adenomatoid tumours: 30% of all paratesticular tumours  
→ restricted to epididymis, tunica, and cord in men – uterus, tubes, and ovary in females

### **What is the etiology of adenomatoid tumours?**

- origin unknown  
→ reaction to injury or inflammation  
→ specialized hemangioma or lymphangioma

### **What is a common histologic feature of adenomatoid tumours?**

- presence of vacuoles in epithelial cells: may replace most of cytoplasm of cells

### **What is the behaviour of adenomatoid tumours?**

- benign: never been a single case of mets → tx w/ excision

### **What is the treatment of tumours of the spermatic cord?**

- explore: if benign, simple excision
- if malignant, radical orchiectomy w/ high ligation of cord

### **What are the advantages of partial orchiectomy?**

- avoids unnecessary orchiectomy for benign disease
- cure of primary if avoid implantation and local recurrence
- preservation of androgen function (esp. in solitary testis)
- preservation of fertility
- psychosocial and cosmetic

### **What are the indications/eligibility criteria for partial orchiectomy?**

- bilateral tumours
- solitary testis
- pt preference after informed consent

### **Can necrosis/fibrosis be predicted in the post-chemo residual retroperitoneal mass?**

- more likely if:
  - absence of teratoma in primary tumour
  - >90% reduction in volume w/ chemotherapy
  - normal pre-chemo markers
  - presence of embryonal in primary
  - <2cm residual mass
- not possible: operate on anyone w/ a residual mass

### **What are the reasons to operate on a teratoma?**

- resistance to chemo
- local invasion

### **What is the differential diagnosis of gynecomastia?**

- NB. Gynecomastia occurs when T/E ration altered
- Physiologic
  - Newborn (placental estrogens)
  - Adolescent (plasma estradiol level reaches adult level before adult T levels are attained)
  - Aging



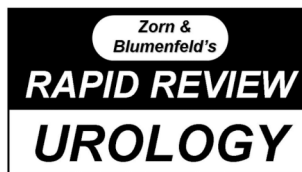
## Chapter 81 Questions - Testis Ca.docncer

- decreased plasma T concentration
- increased conversion of androgen to estrogen
- increased plasma T binding globulin and decrease in free T
- decreased T:estrogen ratio
- Pathologic
  - deficient T production
    - congenital anorchia
    - secondary testicular failure: orchitis, trauma, castration, neurologic and granulomatous disease, renal failure
    - Klinefelters
    - defects in T synthesis
  - deficient T action: AIS, Reifenstein's
  - increased estrogen secretion
    - true hermaphroditism
    - testicular tumour (Leydig cell, Sertoli cell)
    - lung carcinoma
  - increased peripheral conversion of estrogen
    - increased substrate: adrenal disease, liver disease, starvation, thyrotoxicosis
    - increased aromatase (obesity)
  - drugs
    - inhibitors of T synthesis and/or action
      - ◆ anti-androgens: steroidal (cyproterone acetate) or non-steroidal (flutamide, etc.)
      - ◆ spironolactone
      - ◆ cimetidine
    - estrogens: DES, BCP, digitalis, marijuana, heroin
    - gonadotropins
    - unknown mechanisms (busulphan, ethionamide, isoniazid, methyldopa, TCA)

### Discuss the mechanism of action and side effects of BEP.

| Drug                             | Mechanism                                | Cell cycle specific? | Side Effects   | Indication                              |
|----------------------------------|--|----------------------|--|---|
| Antibiotic<br>Bleomycin          | Single-strand scissoring of DNA          | No                   | <ol style="list-style-type: none"> <li><b>NO BM</b></li> <li>Pulmonary fibrosis</li> <li>Alopecia</li> <li>XRT-sensitization</li> <li>Dermatitis</li> <li>Mucositis</li> <li>Tissue necrosis</li> <li>Anaphylaxis</li> <li>Fever</li> <li>Raynaud's</li> </ol> | Testis, neuroblastoma, penis            |
| Antimitotic<br>Etoposide (VP-16) | Mitotic arrest, inhibits DNA replication | Yes, for M phase     | <ol style="list-style-type: none"> <li>BM</li> <li>NV</li> <li>Alopecia</li> <li>Ileus</li> <li>Bronchospasm</li> <li>Hypotension</li> <li>Nephrotoxicity</li> <li>2<sup>nd</sup> malignancy (leukemia)</li> </ol>   | Testis                                  |
| Unclassified<br>Cisplatin (DDP)  | DNA X-linkage and alkylation             | No                   | <ol style="list-style-type: none"> <li>BM</li> <li>NV</li> <li>Otoxicity (high freq hearing loss)</li> <li>Nephrotoxicity (force</li> </ol>  | Bladder, testis, prostate, and ? kidney |

- hydration, avoid gent, NOT  
with CRF)
5. alopecia
  6. Mg leak with seizures
  7. Ca leak
  8. Neurotoxic
  9. Raynaud's
  10. Anaphylaxis
  11. 2<sup>nd</sup> malignancy
  12. hypercholesterolemia
  13. hyperuricemia
-



## **Chapter 82**

### **• Surgery of Testicular Tumours •**

---

#### **What percent of patients w/ testis tumors present w/ sx of mets?**

- 20%: back/abdo pain, wt loss, neck mass, gynecomastia, breast tenderness  
→ due to delay in dx: mean duration of 26 weeks prior to dx

#### **Describe the technique of radical orchiectomy.**

- 5-7cm oblique incision in inguinal area 2cm above pubic tubercle
- incise Camper's and Scarpa's to level of external oblique
- incise external fascia aponeurosis to level of internal ring
- identify ilioinguinal nerve
- isolate and occlude spermatic cord w/ Penrose or non-crushing clamp
- deliver testis into field and divide gubernaculum
- mobilize cord 1-2cm inside internal ring and individually ligating vas and cord vessels  
→ use long silk that can be used to identify stump of cord
- place testicular prosthetic if necessary
- close external oblique w/ 2-0 Prolene, Scarpa's, skin

#### **What is the most common complication of radical orchiectomy?**

- bleeding: scrotal or retroperitoneal hematoma

#### **What are the options for treatment if scrotum is violated?**

- low stage seminoma: extend field of radiation to include ipsilateral groin and scrotum
- low stage NSGCT: scrotal scar should be widely excised with spermatic cord remnant at time of RPLND  
→ cannot use surveillance in T1 NSGCT if scrotum violated
- hemiscrotectomy not needed if full-dose platinum chemo

#### **What are the favourable selection criteria that can be used to determine if a patient is eligible for partial orchiectomy?**

- organ confined disease w/ size < 2cm
- -ve post resection biopsies of tumour bed (-ve frozen section)
- absence of intratubular germ cell neoplasia in the remaining testicular parenchyma
- orchiectomy under cold ischaemia w/ avoidance of spillage or contamination
- compliance?

#### **Describe the lymphatic drainage of the testicle.**

- R testis: interaortocaval LN, then precaval and paracaval LN
- L testis: L para-aortic and preaortic LN, then interaortocaval LN
- 4-8 lymphatic vessels that accompany the spermatic vessels through the internal ring into the retroperitoneum  
→ fan out at the point where gonadal vessels cross anterior to ureter  
→ some drain directly into a LN on the anterior surface of the proximal 1/3 of the external iliac
- contralateral spread more common from R to L, usually associated w/ large volume disease

#### **What is the lymphatic drainage of the epididymis and scrotum?**

- epididymis: external iliac
- scrotum: inguinal LN

#### **What are the major complications of extensive suprahilar LN dissection?**

- increased pancreatic and renovascular complications  
→ suprahilar mets are rare in low-stage NSGCT  
→ perform only for residual hilar/suprahilar masses post-chemo

#### **What is the most consistent long-term morbidity of standard bilateral RPLND?**

*Rapid Review Urology – Study Notes (Kevin C. Zorn & Aaron Blumenfeld, 6/2006©)*

## Chapter 82 Questions - Testis OR.doc

- loss of anterograde ejaculation

### What is required for anterograde ejaculation?

- closure of BN
  - sympathetic fibers close BN
- seminal emission
  - sympathetic fibers that mediate seminal emission originate from T12 to L3
  - form hypogastric plexus near takeoff of IMA just above aortic bifurcation
  - travel via pelvic plexus to innervate the seminal vesicles, vas, prostate, BN
- ejaculation
  - pudendal somatic innervation from S2-4 relax EUS, and cause rhythmic contractions of bulbospongiosus and perineal muscles

### What ganglia are most important to preserve in maintaining anterograde ejaculation?

- paravertebral sympathetic ganglia, post-ganglionic sympathetic fibers T12-L4, and their convergence at the hypogastric plexus

### Describe the possible approaches for exposing the retroperitoneum.

- thoracoabdominal
  - torqued position: lower extremities and pelvis supine, chest and upper extremities rotated
  - OR table hyperextended
  - incision obliquely over 8<sup>th</sup> or 9<sup>th</sup> rib and curves down as a paramedian incision to pubic ramus
  - subperiosteal rib resection
  - divide ipsilateral rectus muscle
  - diaphragm divided, peritoneum mobilized, pleural space entered
  - retroperitoneum exposed to the level of the contralateral ureter
- transabdominal
  - Foley catheter, NG tube
  - midline incision from xiphoid to 2cm above pubis
  - linea alba and peritoneum opened
  - falciform ligament divided b/w silk sutures or excised en bloc w/ properitoneal fat
    - prevents hepatic capsular tears
  - omentum and transverse colon displaced superiorly
  - small bowel reflected to R, incision made in posterior peritoneum medial to IMV
    - incision continued superiorly to ligament of Treitz, and superomedially to duodenojejunal flexure
  - look for avascular plane b/w IMV and L gonadal vein
  - incision in posterior parietal peritoneum continued inferiorly along medial aspect of small bowel mesentery
  - continued around cecum, up R paracolic gutter to foramen of Winslow
  - duodenum is Kocherized
  - many lymphatics superior to L renal vein: must be clipped or ligated
  - vessel loops placed around ureters, retracted laterally
  - ipsilateral gonadal vein mobilized from its insertion in IVC or L renal vein to internal ring
  - adrenal, spermatic, lumbar vessels tied w/ 3-0 silk and divided

### What aberrant vessels are often encountered in an RPLND?

- accessory renal artery: 20%
- retroaortic L renal vein: 2-3%

### Describe the process of lymphadenectomy in RPLND.

- split and roll technique
  - R gonadal vein ligated at IVC, tissue rolled laterally off IVC
  - lumbar veins dissected and doubly ligated w/ 3-0 silk
  - anterior split on aortic surface carried inferiorly to common iliac bifurcation
  - identify IMA: can be sacrificed if marginal colonic artery present
  - ligate gonadal arteries early to prevent subadventitial hematoma
  - retract interaortocaval lymphatic tissue medially and laterally, and lumbar arteries are divided and ligated w/ 3-0 silk
  - R and L renal arteries are skeletonized, and lymphatic tissue is separated from the psoas and anterior spinous ligament
  - inspect bowel and mesentery for injury
  - approximate posterior parietal peritoneum w/ interrupted 3-0 silk

## Chapter 82 Questions - Testis OR.doc

### What is a common post-op hemodynamic finding after RPLND?

- postop tachycardia due to sympathetic discharge

### Who are appropriate candidates for nerve-sparing technique?

- clinical stage I and low-volume stage II
- subset of pts undergoing postchemo RPLND

### What are the most important nerves for preserving antegrade ejaculation?

- those arising from L3-4 ganglia

### What are the indications for primary chemotherapy in pts w/ stage II NSGCT?

- pts w/ suprahilar, retrocrural, pelvic, or inguinal lymphadenopathy
- contralateral or multifocal disease
- back pain
- elevated serum tumour markers

### What is the relapse rate for patients w/ high-volume nodal disease?

- 50-90%
  - should get platinum based chemo

### Which patients are candidates for only 2 cycles of BEP after RPLND?

- pts who are completely resected and are clinically free of disease after RPLND

### How many men w/ testicular cancer have subnormal pretreatment SAs?

- 60%
  - lower total sperm counts, higher FSH

### What is the success rate of nerve-sparing RPLND?

- 95-98%

### What is the pre-op preparation for a patient to undergo RPLND?

- tumour markers, CBC, lytes, Cr
- pulmonary function testing for all pts to have bleomycin
- delay OR after chemo by 3-4 weeks: allow WBC > 3.5, and platelet > 100K

### What complication is to be watched for in pts receiving bleomycin?

- restrictive pulmonary fibrosis due to alveolar edema and increased collagen deposition
- will increase susceptibility to alveolar edema w/ pts exposed to high oxygen levels w/ fluid overload (57%)
  - meticulous management of perioperative fluids

### How can one determine if a post-chemo CT abdo is "normal"?

- size of LN: either 10mm or 20mm have been used
- attenuation values: low attenuation values more likely to represent necrosis

### What is the role of adjuvant chemo after complete resection of viable GCT after salvage chemotherapy?

- no benefit

### What are the advantages of complete resection of teratoma?

- teratoma may grow, obstruct, or invade adjacent structures and become unresectable: "growing teratoma syndrome"
- risk of malignant transformation: 6-8%
  - usually RMS or carcinoma
- may result in late recurrence
- risk of recurrent GCT

### What is the cure rate of recurrent GCT to ifosfamide-based salvage chemo?

- 25%

### Which subsets of patients are at higher risk of relapse after a post-chemo RPLND?

- pts undergoing post-chemo RPLND after salvage chemo (fail to achieve CR to standard cisplatin based chemo)

## Chapter 82 Questions - Testis OR.doc

- lower rates of complete resection
- "desperation" postchemo RPLND (elevated tumour markers)
- pts deemed unresectable: 90% relapse, 21% survive
- "redo" postchemotherapy RPLND: 50% relapse
  - severely disadvantaged, despite other RF

### What adjunctive surgical procedures are occasionally necessary to achieve complete resection of retroperitoneal masses?

- en bloc nephrectomy: most common
- en bloc resection of a great vessel

What is the best surgical technique for the management of a residual mass post-chemo?

- standard bilateral RPLND
- cannot resect residual mass w/o RPLND

### What factor gives the highest prediction that necrosis will be found in a chest recurrence?

- necrosis in the retroperitoneum
  - **must resect all pts w/ thoracic masses regardless of size**
  - can be performed simultaneously

### What complications occur in RPLND?

- Intra-operative
  - anesthetic: aspiration, failure to achieve airway, bleomycin toxicity, MI, CVA, etc.
  - surgical
    - Vascular injury
      - ◆ renovascular injury in 2-3% → renovascular htn
      - ◆ hemorrhage, need for graft, need for transfusion
    - GU injury: nephrectomy, ureteral injury
    - Nerve injury: sympathetic chain, genitofemoral nerve
    - GI injury: duodenal, hepatic, splenic, pancreatic injuries
- Post-operative
  - Early
    - GI: prolonged ileus, SBO in 2-3%, GI bleed
    - Lymphatic
      - ◆ lymphocele
      - ◆ chylous ascites: 2-3%
        - medium chain TG diet + TPN: does not promote formation of chylomicrons, reducing the intestinal lymph secretion
    - secondary hemorrhage, hematoma
    - pulmonary: atelectasis, pneumonia, ARDS
      - ◆ bleomycin toxicity: pulmonary fibrosis
    - CVS: MI/CVA, DVT/PE
    - Infectious: wound infection, abscess, seroma, dehiscence, hernia, UTI
    - Mortality <1%
  - Late
    - SBO
    - fistula
    - fertility: emission and ejaculation failure
    - paraspinal ischemia from ligation of lumbar arteries during aortic mobilization

### What are the RF for developing chylous ascites?

- IVC resection, suprahilar dissection, hepatic resection

### What are the presenting signs of chylous ascites?

- abdo distension, prolonged ileus, abdo fluid wave, pleural effusion, chylous leakage from the incision

### How does one investigate and treat chylous ascites?

- perform CT w/ paracentesis to diagnose and treat initially
- diuretics and medium chain triglycerides + TPN

### What is the mechanism of infertility post-chemotherapy?

**Chapter 82 Questions - Testis OR.doc**

- platinum causes dysfunction of Leydig's and Sertoli's cells
- nadir in spermatogenesis in 10-14 months
- return to baseline for majority by 3 years
- no increase in birth defects after treatment for testis cancer







## **Chapter 83**

### **• Tumours of the Penis •**

---

#### **What is your differential diagnosis for a penile lesion?**

- Benign lesions
  - Noncutaneous lesions
    - congenital and acquired cysts
    - retention cysts
    - syringomas
    - neurilemmomas
    - benign tumours of the supporting structures: fibromas, neuromas, lipomas, myomas
    - penile pseudotumours: develop after self-injection or implantation of FB
    - phlebitis, lymphangitis, angitis
  - Cutaneous lesions
    - pearly penile papules
    - hirsute papillomas
    - coronal papillae
    - Zoon's erythroplasia
- Premalignant cutaneous lesions
  - cutaneous horn
  - pseudoepitheliomatous micaceous and keratotic balanitis
  - BXO
  - leukoplakia
  - CIS
  - condylomata accuminatum
- Viral related lesions (?premalignant)
  - condyloma accuminatum
  - Bowenoid papulosis
  - Kaposi's sarcoma
- SCC
- Bushke-Lowenstein tumour
- Nonsquamous malignancies
  - BCC
  - melanoma
  - sarcoma
  - Paget's disease
  - surface adenosquamous carcinoma
  - lymphoreticular malignancy
  - mets

#### **What are retention cysts of the penis?**

- arise from the sebaceous glands located on the mucosal surface of the prepuce and skin of the penile shaft

#### **What are syringomas?**

- benign tumours of the sweat glands: may become large and symptomatic

#### **What are pearly penile papules?**

- acral angiofibromas

#### **What is Zoon's erythroplasia?**

- a benign shiny erythematous plaque or erosion
- demonstrates normal cell layers on biopsy but a dense plasma cell infiltrate
  - treat w/ circumcision or CO<sub>2</sub> laser

## Chapter 83 Questions - Penile Ca.docnccer

### What is a penile cutaneous horn?

- overgrowth and cornification of the epithelium growing over a preexisting skin lesion (wart, nevus, traumatic abrasion, ca)
- presence of extreme hyperkeratosis and acanthosis
  - treat w/ excision w/ a margin of normal tissue
  - may evolve into SCC

### What is the treatment of BXO?

- topical steroid cream, injectable steroids, or surgical excision

### What is pseudoepitheliomatous micaceous and keratotic balanitis?

- premalignant lesion that presents as hyperkeratotic growth on glans
- tend to recur
  - treat w/ excision, laser, cryo

### What is leukoplakia?

- solitary or whitish plaque that involves meatus
  - micro: hyperkeratosis, hypertrophy of rete pegs w/ dermal edema and lymphocytic infiltration
- treat w/ elimination of chronic irritation, circ

### What disorders are associated w/ leukoplakia?

- in situ SCC
- verrucous cancer of the penis

### What % of condyloma acuminatum (genital warts) involve the urethra?

- 5%

### What histologic cell type is pathognomonic for HPV infection?

- the **koilocyte**: a cell characterized by an empty cavity surrounding an atypical nucleus

### What subtypes of HPV are associated w/ low-grade dysplasia and which are associated w/ malignancy?

- low grade dysplasia and gross condylomata: 6, 11, 42, 43, 44
- malignancy: 16, 18, 31, 33, 35, 39

### What is the significance of the tumour virus transforming proteins E6 and E7 from HPV types 16 and 18?

- may target tumour suppressor gene products pRb and p53 and cause penile cancer

### How can subclinical condylomatous disease be detected?

- 5% acetic acid solution applied to the penis followed by inspection w/ magnifying glass
  - lesions turn white

### What are the potential management options of condyloma acuminatum?

- **always biopsy large lesions prior to treatment: podophyllin may induce changes suggestive of SCC**
- Medical
  - topical podophyllin: 0.5%-1% solution x 2-6 weeks
    - normal skin disrupted by podophyllin: careful supervision
  - trichloroacetic acid
  - 5-FU cream for intraurethral lesions: 2-5% cream
  - interferons: IFN- $\alpha_{2b}$
- Surgical
  - fulgurization and excision for larger lesions: prevents maceration from medical therapy w/ secondary infection
  - laser
  - surgical debulking w/ ureteral resectoscope for large intraurethral lesions
    - low power to prevent urethral stricture

### What is bowenoid papulosis?

- a benign lesion that mimics CIS of the penis
  - usually pigmented, range from 2-30mm in diameter
  - dx by biopsy

### **Chapter 83 Questions - Penile Ca.docncer**

- treatment: electrodesiccation, cryo, laser, topical 5-FU, excision + grafting

#### **What is Kaposi's sarcoma?**

- tumour of the reticuloendothelial system
- presents as cutaneous neovascular lesion or ulcer w/ bluish discoloration

#### **What is the etiology of Kaposi's sarcoma in HIV?**

- HHV8

#### **What are the subtypes of Kaposi's sarcoma?**

- classic Kaposi's
  - in pts w/o immunodeficiency, indolent course: usually eastern European, Italian, Jewish
- immunosuppressive treatment-related Kaposi's
  - in pts on immunosuppression, reverses w/ dose modification
- African Kaposi's
  - in young males
- HIV-related Kaposi's: 7000X increased risk

#### **What is the treatment for penile Kaposi's?**

- localized surgical excision
  - classic and immunosuppressive treatment related Kaposi's rarely associated w/ diffuse involvement
- external beam radiation

#### **What are the characteristics of the Buschke-Lowenstein tumour (verrucous carcinoma, giant condyloma accuminatum)?**

- invades locally and destroys by compressing adjacent tissue
  - always remains superficial, and never invades adjacent tissue
  - aggressive growth, bleeding, discharge, odor
- **no signs of malignant change, and mets do not occur**

#### **What is the treatment for Buschke-Lowenstein tumour?**

- excisional biopsy
  - no effect w/ podophyllin, 5-FU, radiation
  - recurrence is common → need close follow up
- rads: not effective → associated w/ rapid malignant changes
- IFN + laser

#### **What is the difference b/w Bowen's disease and erythroplasia of Queyrat?**

- CIS of the penis
  - erythroplasia of Queyrat: if involves glans, prepuce, penile shaft
  - Bowen's disease: if involves remainder of genitals or perineal region
- red, velvety, marginated lesion of glans
  - may ulcerate and cause pain/discharge
- no visceral malignancy w/ either

#### **What is the treatment of penile CIS?**

- local excision: if small and noninvasive
- circumcision if on prepuce
- fulguration: may result in recurrence
- radiation
- topical 5-FU: good cosmesis

#### **What are the RF for invasive penile cancer?**

- uncircumcised male or phimosis
  - chronic irritative effects of smegma
  - more frequent if circ delayed until puberty: no protection w/ adult circ
- HPV infection: 16, 18, 31, 33, 35, 39
  - type 16 most common
  - related to # of lifetime sexual partners
- cigarette smoke, chewing tobacco, snuff

## Chapter 83 Questions - Penile Ca.docncer

- penile tears or rashes

### Describe the natural hx of invasive penile cancer.

- 0.4-0.6% of all malignancies
  - increasing in Finland, US, India, Asia
  - peak around age 80
- begins w/ small lesion, gradually extends to involve entire glans, shaft, and corpora
  - penile autoamputation may result
- lesions > 5cm or those extending > 75% of the shaft: increased risk of mets
  - Buck's fascia acts as a temporary barrier
  - mets to regional femoral and iliac nodes
  - drain to superficial inguinal nodes, which drain to deep inguinal nodes
- metastatic enlargement of the regional nodes leads to skin necrosis, chronic infection, death
- distant mets to lung, liver, bone, brain in 1-10%
- death if untreated in 2 yrs for most

### What is involved in the workup of a pt w/ a penile mass?

- Hx
  - race
  - smoker
  - hygiene
  - phimosis
  - STDs: HPV
  - lesion:
    - shallow ulcer
    - foul odor
    - discharge
    - mass
    - hemorrhage
    - urinary retention
    - fistula
    - pelvic mass
  - markers of advanced disease
    - weakness, wt loss, fatigue, malaise
    - blood loss
- Physical
  - General appearance
  - Abdo masses, bladder, and CVAT
  - External genitalia: size of lesion, evidence of invasion
  - Inguinal adenopathy
  - Evidence of infection/cellulitis
- Labs
  - Urine R&M C&S
  - CBC, lytes, Cr, BUN, ALP, Ca, Mg, Phos, albumin, AST, ALT, ALP, BR, PT, PTT
    - WBC: anemia, leukocytosis
    - albumin: hypoalbuminemia
    - Ca profile: hypercalcemia → due to bulk of disease
      - ◆ treat w/ bisphosphonates
- Biopsy/excision of mass
  - mandatory prior to any tx
    - may need dorsal slit to reach mass
    - no harm from biopsy reported
- Imaging
  - CXR
  - CT abdo/pelvis for nodes
  - Bone scan
  - MRI/CT abdo
    - if palpable inguinal l/a or if unreliable physical exam
- Node dissection
  - superficial dissection or biopsy

## Chapter 83 Questions - Penile Ca.docnccer

What are the options for the treatment of primary in a penile mass?

- If truly invading corpus spongiosum, then stage T2
- To treat primary, options include:
  - Moh's micrographic surgery
  - Laser ablation with CO2 or Nd-YAG laser
  - Interstitial XRT
  - Partial penectomy with 2cm margin
  - Complete penectomy if too large or proximal for partial

What are the histologic subtypes of penile SCC?

- superficially spreading SCC: inguinal mets in 42%
  - most frequent
- vertical growth carcinoma: inguinal mets in 80%
- verrucous carcinoma: no inguinal mets
- multicentric carcinoma: inguinal mets in 1/3

What histologic features of SCC stratify patients for prognosis?

- grade: Broder's classification → based on keratinization, nuclear pleomorphism, mitotic figures, and others
  - lack of correlation b/w grade and survival
- modification by Maiche (1991)
  - overall score based on degree of keratinization, mitotic figures / HPF, cellular atypia, and presence of inflammatory cells
  - 80% 5 year survival for grade 1, 50% for grade 2-3, 30% for grade 4
- vascular invasion: significant prognostic factor
  - important predictor of +ve LN

What is the role of imaging studies for penile SCC?

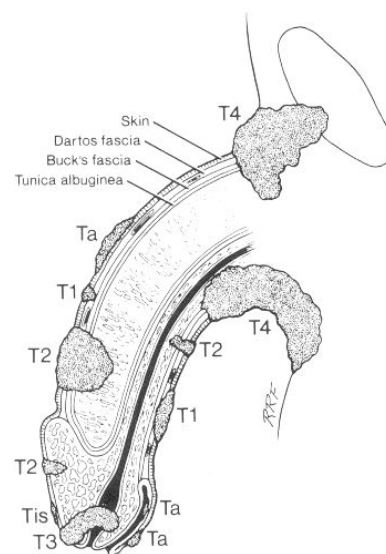
- for small volume glanular lesions, imaging studies not used
  - if suspect invasion of corpora, US and contrast-MR can be helpful if organ-sparing surgery is considered
    - cannot define internal architecture of normal-sized LN
  - US: can detect corporal invasion
  - CT: poor resolution, not useful
    - sensitivity 36%, specificity 100% for LN enlargement
  - lymphangiography: not useful
  - bone scan, CXR: used if suspect mets

What are the most common sites for distant mets in penile ca?

- lung
- bone
- liver

Describe the AJCC staging system used for penile SCC.

- T stage
  - Tx: tumour cannot be assessed
  - T0: no evidence of primary
  - Tis: CIS
  - Ta: noninvasive verrucous carcinoma
  - T1: invades subepithelial connective tissue
  - T2: invades spongiosum or cavernosum
  - T3: invades urethra or prostate
  - T4: invades other adjacent structures
- Lymph nodes
  - Nx: regional nodes cannot be assessed
  - N0: no regional LN mets
  - N1: mets in a single regional LN
  - N2: mets in **multiple or bilateral superficial LN**
  - N3: mets in **deep inguinal or pelvic LN**, unilateral or bilateral
- Mets
  - Mx: cannot be assessed



## Chapter 83 Questions - Penile Ca.docncer

- M0: no distant mets
- M1: distant mets

### Describe the stage groupings for penile cancer.

- Stage I: **T1N0M0**
- Stage II: **T2N0-1M0, T1N1M0**
- Stage III: **T3N0-2M0, T1-2N2M0**
- Stage IV: **T4N0-3M0, T0-4N3M0, T0-4N0-3M1**

### What are the differences b/w the 1978 and 1997 TNM systems for penile cancer staging?

- T stage: T1-3 based on size of primary (<2cm, 2-5cm, >5cm)
- N stage: based on laterality and mobility of LN

### Describe Jackson's classification for carcinoma of the penis. → original staging sx

- Stage A: confined to glans, prepuce, or both
- Stage B: tumour on shaft
- Stage C: operable inguinal mets
- Stage D: inoperable inguinal mets, or involving adjacent structures, or distant mets

### What are the indications for a formal inguinal node dissection with penile cancer?

- Absolute
  - palpable adenopathy after 6wks of antibiotics
  - development of positive adenopathy after period of surveillance
  - +ve sentinel node
  - +ve superficial node dissection
- Relative
  - impalpable nodes with penile cancer (particularly if high T stage or grade)

### What nodal criteria predict for long-term survival after inguinal lymphadenectomy?

- minimal nodal disease (0-2 LN)
  - no inguinal mets: 50-100% (mean 73%) 5yr survival
  - resected inguinal mets: 0-86% (mean 60%) 5yr survival
- unilateral involvement
- no extranodal extension of cancer
- absence of pelvic nodal mets

### What are the complications of inguinal, pelvic or retroperitoneal lymphadenectomies?

- phlebitis: 9%
- DVT/PE
- wound infection: 15%
- flap necrosis: 50%
- lymphedema of the scrotum and lower limbs: 50%
- seroma: 16%
- lymphocele
- femoral vessel erosion
- femoral nerve injury
- no complications only in 18%

### What is the evidence of immediate vs. delayed inguinal lymphadenectomy in patients w/o palpable LN?

- 5 series report improvement in survival for patients undergoing early vs. delayed dissection
- 4/5 series show that **delayed dissection rarely salvages pts who have recurrence**

### How can one divide patients into high- vs. low-risk groups for LN mets?

- tumour histology
  - little or no risk: CIS, verrucous carcinoma, no vascular invasion
  - high risk: vascular invasion
    - absent in all T1 tumours
- tumour stage
  - low risk: Tis, Ta, T1G1-2

### Chapter 83 Questions - Penile Ca.docnccer

- high risk: corporal invasion (T2 or greater)
  - +ve LN in 75% if vascular invasion present, but only 25% if absent
- tumour grade
  - low risk: G1-2
  - high risk: G3

#### What is the incidence of mets in pts w/ high- vs. low-risk disease?

- high-risk: 50%
- low-risk: <10%

#### What options are available to investigate LN of pts w/ high risk disease?

- fine-needle aspiration cytology (FNAC)
  - experience limited
  - pedal/penile lymphangiography w/ aspiration under fluoro
  - 20% false -ve
- node biopsy
- sentinel LN biopsy (SLNB)
- extended sentinel LN biopsy (ESLNB)
  - if SLNB -ve for tumour, mets to other ilioinguinal nodes do not occur
  - false -ve rate 10-50%
- intraoperative lymphatic mapping (IOLM)
  - inject either blue dye or gamma emission into lesion
- superficial dissection
  - remove LN superficial to fascia lata
  - no LN +ve deep to fascia lata if superficial nodes -ve on frozen section
- modified complete dissection

#### How good are SLNB, ESLNB, and node biopsy?

- unreliable: not recommended

#### Should inguinal lymphadenectomy be bilateral in patients w/ unilateral lymphadenopathy at initial presentation?

- Yes: crossover of penile lymphatics

#### Should inguinal lymphadenectomy be bilateral in patients w/ unilateral lymphadenopathy some time after initial presentation?

- No: disease-free interval from observing normal side

#### Should pelvic lymphadenectomy be performed in patients w/ +ve inguinal LN?

- not known
  - pts w/ +ve inguinal LN at increased risk for spread to pelvic LN
  - may be used to stage pts that undergo potential curative inguinal lymphadenectomy and to decide if need chemo

#### Describe the algorithm used to manage regional LN disease in penile cancer.

- Tis, Ta (risk of mets very low, even anecdotal)
  - LN -ve: observe
  - LN +ve: 4 weeks of antibiotics, reassess
    - LN persistently +ve: FNAC
      - ◆ FNAC -ve: excisional biopsy of single node
      - ◆ FNAC +ve or excisional biopsy +ve
        - ♦ ipsilateral deep inguinal and pelvic LN dissection + contralateral superficial dissection / complete modified
- T1G1-2 (risk of mets < 10%)
  - LN -ve: observe
  - LN +ve: 4 weeks of antibiotics, reassess
    - LN persistently +ve: treat as high risk
- stage T2 or greater, presence of lymphovascular invasion, G3 disease (high risk of mets: 50-70%)
  - LN bilaterally -ve: bilateral superficial inguinal dissection or complete modified dissection
    - do frozen section at OR: if frozen section +ve, continue w/ ipsilateral deep inguinal and pelvic LN dissection
  - LN unilaterally +ve, mobile, and < 4cm: ipsilateral deep inguinal and pelvic LN dissection w/ contralateral superficial dissection / complete modified dissection

### Chapter 83 Questions - Penile Ca.docnccer

- if +ve, ipsilateral deep, inguinal, and pelvic LN dissection
- LN bilaterally +ve, mobile, and < 4cm: consider FNAC
- FNAC –ve: bilateral superficial inguinal dissection or complete modified dissection
  - ◆ do frozen section at OR: if frozen section +ve, continue w/ ipsilateral deep inguinal and pelvic LN dissection
- FNAC +ve: bilateral ilioinguinal dissection
  - ◆ **add adjuvant chemo if > 2 +ve LN, extranodal extension, or +ve pelvic LN**
- LN fixed, > 4cm, or pelvic LN mets seen on preop imaging: combination chemo
- if responds: aggressive surgical treatment (to minimize local morbidity)
- progresses: resect if palliative vs. salvage chemo/rads

### What are the arguments for and against early inguinal LN dissection?

- For
  - corporal involvement increases risk of LN mets
  - high rate of false -ve LN status on clinical evaluation (up to 25%)
  - bad prognosis if LN mets not resected
  - resection of +ve LN potentially curable with long term survival
  - better survival with early resection of micromets than late resection of macromets
  - complications of resection of micromets should be lower than resection of macromets
- Against
  - unnecessary LN dissection in 75% of patients with high morbidity
  - no apparent survival benefit in 5 year survival of early adjunctive LN dissection vs. late therapeutic LN dissection
  - significant morbidity (phlebitis, PE, wound infection, flap necrosis, lymphedema)

### What are the disadvantages to radiation therapy for a primary lesion?

- SCC is radioresistant
  - high dose (60 Gy) can cause urethral fistula, stricture, stenosis, penile necrosis, pain, edema
  - penile necrosis: 10%
  - urethral stricture: 30%
- secondary penectomy may be required
- infection prevents effect of rads
  - partial penectomy offers a prompt and effective management
- administered over 3-6 weeks, several months of morbidity
- if fails, must do prompt penectomy to avoid jeopardizing survival
- difficult to distinguish b/w postradiation scar, ulcer, fibrosis from recurrent cancer
  - may require repeated biopsies

### What are the indications for radiation treatment of penile ca?

- young individuals w/ small (2-4cm) superficial exophytic noninvasive lesion on glans/coronal sulcus
  - 90% response rate
- pts refusing surgery
- pts w/ inoperable tumour or distant mets that require local treatment and want to retain their penis
- failure of 5-FU in CIS

### What are the results of radiation therapy for small superficial lesions?

- successful: 90% control
  - significant complications: penile necrosis (10%), urethral stricture (30%)

### What is the result of brachy for penile cancer?

- local control in 80%
- long term survival in 75-80%
  - prognosis not altered if surgery performed promptly after a failure
  - more frequently have LN+ve

### What is the role for radiation of the inguinal LN?

- controversial: groins tolerate radiation poorly
  - inaccurate clinical staging
  - lack of histologic confirmation of LN mets
  - adjuvant radiation: controversial as well
  - due to tissue changes after rads, clinical evaluation of the groins is difficult



### Chapter 83 Questions - Penile Ca.docncer

- complications of groin dissection after rads are significant
- **overall not as effective as LN dissection**, but may be useful for palliation (inoperable fixed and ulcerative inguinal LN)
  - infectious l/a reduces effectiveness of rads and increases complications

### What chemotherapeutic agents have been used to treat penile ca?

- cisplatin
  - single agent PR: 23%
- bleomycin
- methotrexate
  - single agent PR: 60%

### What are the combinations of chemotherapeutic agents used to treat penile cancer?

- VBM: vincristine, bleo, MTX
  - increased survival in node +ve pts
- PF: cisplatin, 5-FU
- MPB: MTX, leukovorin, cisplatin, bleo
- PMB: cisplatin, bleo, MTX

### What flaps are useful in groin coverage?

- TFL musculocutaneous transfer unit
- biceps femoral musculocutaneous transfer unit
- vastus lateralis muscle flap
- gracilis musculocutaneous unit
- vertical rectus abdominis muscle flap
- omental flaps

### What is the premalignant fibroepithelioma of Pinkus?

- benign variant of BCC

### What are the primary tumours metastasize to the penis?

- bladder, prostate, rectum: majority
- renal, lung

### What is the most common sarcoma of the penis?

- vascular: hemangioepithelioma > neural > myogenic > fibrous
  - distant and regional mets are rare

### What are the most important prognostic factors for survival in pts w/ penile SCC?

- presence and extent of mets involving the inguinal nodes

### What pathologic criteria are associated w/ long-term survival after attempted curative surgical resection of inguinal mets?

- minimal nodal disease
- unilateral involvement
- no extranodal extension of cancer
- absence of pelvic nodal mets

### How often is palpable l/a associated w/ proven LN mets?

- > 50% of cases, rest due to inflammation
- after 6 weeks antibiotics, 70-86% due to mets

### What is the 5-yr survival of pts after inguinal LN dissection?

- minimal LN mets (<2): 77%
- significant LN mets: 25%

### What pts are at low risk of developing LN mets?

- CIS
- T<sub>a</sub>
- T<sub>1</sub> G<sub>1-2</sub>

## **Chapter 83 Questions - Penile Ca.docncer**

### **Which pts are at high risk of developing LN mets?**

- T2 or greater
- G3 tumours
- vascular invasion
- noncompliant pts

### **Where is the sentinel LN for the penile lymphatics?**

- located superomedial to the junction of the saphenous and femoral veins in the area of the superficial epigastric vein  
→ incision is 2 fingerbreadths inferolateral to pubic tubercle

### **Why is SLNB not recommended?**

- 10% false negative rate
- biopsies directed to specific anatomical area are unreliable in identifying microscopic mets

### **Describe the epidemiology of HPV infection.**

- increases w/ sexual promiscuity: 10-80%
- biphasic age distribution  
→ 1 peak at age 16-35 (increased sexual activity), 2<sup>nd</sup> peak after 75 years (decreased immunity w/ old age)

### **Why is HPV relatively resistant to heating and organic solvents?**

- DNA virus w/ no outer membrane → outer capsule of viral proteins

### **How many HPV subtypes exist?**

- 77 as of 1999

### **How is HPV transmitted?**

- STD: primarily infect epithelial cells

### **What is the function of the E6/E7 genes in HPV?**

- immortalize human keratinocytes on transfection
- E6/E7 oncoproteins interfere w/ cellular tumour suppressor proteins p53 and pRB

### **Where are the typical sites of HPV inoculation, and why does this occur?**

- occurs at the sites of genital micro-trauma: frenulum, coronal sulcus, preputial skin, meatus

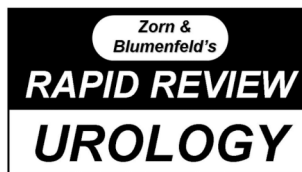
### **How can one classify grade of HPV-related penile lesions?**

- PENIN (penile intraepithelial neoplasia)
  - PENIN I: mild dysplasia
  - PENIN II: moderate dysplasia = bowenoid papulosis
  - PENIN III: severe dysplasia = CIS = Bowen's/erythroplasia of Queyrat

### **Recommendations:**

**HPV and Carcinoma of the Penis – AUA Update XIX #1**

**Penile Cancer: Contemporary Surgical Management of the Inguinal and Pelvic Nodes – AUA Update XXI #33**



## **Chapter 84**

### **• Surgery of Penile and Urethral Carcinoma •**

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#### **What lasers can be used to treat premalignant lesions or CIS of the penis?**

- Nd:YAG: depth of penetration of 3-6mm, can coagulate vessels up to 5mm diameter
- CO<sub>2</sub>: wavelength of 10600nm, absorbed by intracellular water, causing vaporization
- argon: 488-515nm wavelength
- KTP: 532nm wavelength

#### **What penile lesions are adequately treated w/ laser?**

- premalignant lesions
- CIS
- some Ta and T1 penile cancers

#### **What are the advantages and disadvantages of treating penile cancers w/ laser?**

- Advantages
  - destruction of the lesion w/ preservation of normal surrounding structures and function
- Disadvantages
  - inability to determine depth of destruction
  - inability to treat larger lesions
  - lack of histologic demonstration of stage

#### **What is Mohs' micrographic surgery (MMS)?**

- sequential local excision of the primary tumour in thin horizontal layers w/ histologic tracking of residual neoplastic elements
- color coding of excised specimens → construction of tissue maps
- cure rates equivalent to surgery for low-stage tumours
  - 100% for lesions < 1cm, only 50% for lesions > 3cm

#### **What are complications of MMS?**

- meatal stenosis: treat w/ island flaps to reconstruct meatus or VY advancement techniques
- disfigurement of the glans

#### **What are the contraindications to MMS?**

- larger or higher stage lesions

#### **Describe the surgical technique for partial penectomy.**

- Pre-op
  - palpate the inguinal nodes
  - biopsy lesion
  - US or CT pelvis if suspect invasion/mets
- Operative
  - pt is supine
    - lithotomy if total penectomy may be necessary
  - lesion is excluded by a towel or surgical glove
    - suture in place
  - tourniquet applied at the base of the penis
    - 20F red rubber or Penrose drain
  - skin is incised circumferentially
    - ensure 2cm margin is left proximal to lesion
    - attempt to leave 3cm of proximal shaft
  - superficial and deep dorsal vessels are ligated
  - incise Buck's fascia onto tunica albuginea
  - cavernous bodies are divided sharply to the urethra, leaving spongiosum intact

## Chapter 84 Questions - Penile OR.doc

- temporarily release tourniquet to visualize and ligate cavernosal arteries
- send proximal margin for frozen section
- urethra dissected to attain a 1cm distal redundancy
- urethra divided and spatulated on dorsal surface
- corpora secured w/ interrupted sutures opposing the margins of Buck's fascia
- close w/ 2-0 Vicryl, including septum
- tourniquet removed, hemostasis achieved
- approximate spatulated urethra to penile skin to form skin-urethra anastomosis w/ 3-0 or 4-0 chromic or Dexon absorbable sutures, open side up
- redundant skin approximated dorsally
- 18F Silastic catheter and dressing x 24h

### Describe the surgical technique for total penectomy.

- Operative
  - elliptical lesion made around base of penis
  - corpora dissected proximally to suspensory ligament
  - dorsal vessels divided
  - divide urethra distally and retract ventrally to dissect from corpora in bulbar region
  - dissect corpora from attachments at pubic rami
    - crura transected w/ stumps ligated w/ chromic suture
  - 1cm ellipse of skin removed from perineum
  - create tunnel bluntly in perineal tissue
  - transpose urethra through perineum w/o angulation
    - urethra spatulated
    - skin-to-urethra anast
  - primary incision closed transversely to elevate scrotum away from new meatus
  - Penrose drain
- Post-op
  - Foley x 24-48h

### What separates the deep and superficial inguinal lymph nodes?

- fascia lata (deep fascia of the thigh)

### What is the node of Cloquet?

- the most cephalad node of the deep inguinal nodes
- lies within the femoral canal, medial to femoral vein

### What vessels supply the skin of the inguinal region?

- branches of the common femoral artery
  - superficial external pudendal
  - superficial circumflex iliac
  - superficial epigastric artery

### What is the cause of flap necrosis after inguinal LN dissection?

- node dissection requires ligation of the branches of the common femoral artery
- skin flap viability depends on anastomotic vessels in the superficial fatty layer of Camper's fascia

### What are the boundaries of the femoral triangle?

- inguinal ligaments
- sartorius
- adductor longus

### Where is the location of the saphenofemoral junction?

- two finger-breadths lateral and inferior to the pubic tubercle

### What are the options for nodal evaluation and staging in penile cancer?

- sentinel node biopsy
  - utility not confirmed clinically: extensive mets reported w/ -ve sentinel biopsy
- modified (limited) inguinal dissection: for pts w/ clinically -ve nodes or minimally enlarged nodes
- radical ilioinguinal node dissection

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### How does the modified groin dissection differ from the standard dissection?

- skin incision is shorter
- node dissection limited to medial to femoral artery, and inferior to fossa ovalis
- saphenous veins are preserved
- no transposition of sartorius muscle

### What are the borders of an inguinal node dissection for penile cancer?

- Excise all inguinal nodal tissue within this quadrangle:
  - Oblique line from pubic tubercle to ASIS superiorly
  - 15 cm down from lateral border of pubis is medial border
  - 20 cm down from ASIS is the lateral border
  - Adjoining these areas is an 11 cm transverse line inferiorly
- The borders of the FORMAL excision are:
  - Superior: 2cm above inguinal ligament
  - Lateral: sartorius muscle
  - Medial: adductor longus
  - Inferior: junction of sartorius and adductor longus
  - Superficial: leave Camper's fascia and subdermal fat with skin but take Scarpa's
  - Floor = pectineus medially and iliopsoas laterally
  - Fascia lata demarcates superficial from deep nodes
  - Contents = femoral nerve (lateral), artery and vein (medial)
- Border of the MODIFIED excision are:
  - Superior: spermatic cord
  - Medial: sartorius muscle
  - Lateral: femoral artery
  - Inferior: fossa ovale (gap in fascia where greater saphenous vein enters femoral)
  - Differences:
    - Shorter incision (generally 10cm long 1.5cm below groin crease)
    - Saphenous vein preserved
    - Do not transpose sartorius
    - Spare nodes lateral to femoral artery and caudal to fossa ovale

### What are the indications for a formal inguinal node dissection with penile cancer?

- Absolute
  - palpable adenopathy after 6wks of antibiotics
  - development of positive adenopathy after period of surveillance
  - +ve sentinel node
  - +ve superficial node dissection
- Relative
  - impalpable nodes with penile cancer (particularly if high T stage or grade)

### Describe the technique of modified LN dissection.

- 10cm incision 1.5cm below the groin
  - dissect down to level of Scarpa's fascia
- superior flap developed deep to Scarpa's for 8cm
- identify and reflect spermatic cord medially
  - reflect all fibrofatty tissue below this structure superiorly as a "package"
- develop inferior flap for 6cm below the incision
- dissect tissue off fascia lata and fossa ovalis from lateral to medial
  - preserve saphenous vein
- dissect deep nodes around femoral vessels superiorly to level of inguinal ligament and excise
- closed-suction drain

### Describe the technique of radical ilioinguinal LN dissection.

- Pre-op
  - 6 week course of antibiotics
  - bowel preparation
  - elastic support wraps
  - pre-op antibiotics

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- Operative
  - Positioning
    - position w/ involved thigh slightly abducted and externally rotated
    - Foley
    - support and suture scrotum out of field
    - exclude fungating tumour from field by suturing lap sponge to skin around lesion prior to prep
  - Incision
    - oblique or elliptic incision below and parallel to inguinal ligament if require bilateral dissection
    - add lower midline extraperitoneal incision to allow access to pelvic nodes
    - incision extends from ASIS toward pubic tubercle, parallel to inguinal ligament for 4-6cm
      - ◆ bevel out, so skive underneath skin to excise pyramid, w/ base on external oblique aponeurosis
  - dissect out fat and areolar tissue from external oblique aponeurosis and cord to inferior border of inguinal ligament
  - identify femoral artery and vein at apex of femoral triangle, and dissection is continued superiorly
  - divide saphenous vein at saphenofemoral junction
  - dissect anterior and lateral aspects of femoral vessels
    - femoral vessels not skeletonized
  - sartorius muscle mobilized from origin at ASIS
    - transposed or rolled medially to cover femoral vessels
    - origin sutured to inguinal ligament superiorly, margins sutured to muscles of thigh adjacent to femoral vessels
  - femoral canal closed by suturing shelving edge of Poupart's ligament to Cooper's ligament
  - Pelvic lymphadenectomy
    - lower midline extraperitoneal approach
    - inguinal approach
  - Post-op
    - closed-suction drain x 5-7d
    - Foley x 24-48h
    - low-residue diet
    - leg wraps, keep foot of bed elevated
    - anticoagulation

### What is a limitation of the double-incision unilateral approach?

- inability to conveniently excise a previous biopsy scar or areas of cutaneous involvement
  - decreased wound morbidity

### What are the three basic routes to the pelvic LN through an inguinal incision?

- inguinal ligament divided vertically over vessels or at ASIS
- incision of external oblique fascia, reflecting cord cephalad, dividing the inguinal floor from internal ring to pubic tubercle
- incision in anterior abdominal muscles 4-5cm above and parallel to inguinal ligament w/ medial mobilization of peritoneum

### What nodal groups are removed in a PLND for penile cancer?

- distal common iliac, external iliac, obturator nodes

### What are the RF for urethral cancer?

- chronic inflammation
  - frequent STD
  - urethritis
  - stricture
- HPV 16

### What % of men w/ urethral carcinoma had a prior urethral stricture?

- 24-76%

### What is the most common portion of the urethra involved w/ cancer?

- bulbomembranous urethra (60%)
- penile urethra (30%)
- prostatic urethra (10%)

### What are the most common presenting sx of male urethral cancer?

## Chapter 84 Questions - Penile OR.doc

- obstructive voiding sx
- palpable urethral mass
- stricture
- bleeding
- perineal pain
- urethral fistula

### What are the histologic subtypes of male urethral cancer?

- SCC: 80%
- TCC: 15%
- adenocarcinoma/undifferentiated: 5%
- depends on anatomic location
  - prostatic: 90% TCC, 10% SCC
  - penile: 90% SCC, 10% TCC
  - bulbomembranous: 80% SCC, 10% TCC, 10% adeno

### What is the lymphatic drainage of the male urethra?

- anterior urethra
  - superficial and deep inguinal LN
  - external iliac
- posterior urethra
  - pelvic LN

### Describe the staging system for urethral cancer.

- Tumour
  - Tx: cannot be assessed
  - T0: no evidence for primary tumour
  - Ta: noninvasive papillary, polypoid, or verrucous carcinoma
  - Tis: CIS
  - T1: tumour invades subepithelial connective tissue
  - T2: tumour invades sponge, prostate, periurethral muscle
  - T3: tumour invades cavernosa, beyond prostatic capsule, anterior vagina, bladder neck
  - T4: tumour invades any other adjacent organs
- TCC Prostate
  - Tis-pu: CIS involving prostatic urethra
  - Tis-pd: CIS involving prostatic ducts
  - T1: tumour invades subepithelial connective tissue
  - T2: tumour invades prostatic stroma, sponge, periurethral muscle
  - T3: tumour invades cavernosa, beyond prostatic capsule, bladder neck
  - T4: tumour invades any other adjacent organs (bladder)
- Nodes
  - Nx: regional LN cannot be assessed
  - N0: no regional LN
  - N1: single LN < 2cm
  - N2: single or multiple LN 2-5cm
  - N3: LN > 5cm
- Mets
  - Mx: mets cannot be assessed
  - M0: no distant mets
  - M1: distant mets

### What is involved in the staging of urethral cancer?

- EUA
  - cystoscopy
  - bimanual palpation
- TUR or needle biopsy
- cytology
- sigmoidoscopy and barium enema
- CXR, labs (LFT, Ca profile)
- CT/MRI to determine local extent

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→ MR very helpful in determining invasion of the corpora cavernosae

### How does location of urethral cancer affect treatment?

- anterior urethral cancer: better treated w/ surgery
- posterior associated w/ extensive local invasion: treat w/ palliation  
→ not very likely to cure

### What are the options for treatment of carcinoma of the distal urethra?

- superficial, papillary, CIS: TUR and fulguration
- invasive tumour: partial penectomy w/ 2cm -ve margin
- proximal tumour: total penectomy
- penile sparing surgery: urethrectomy w/ PU
- inguinal LN dissection if palpable LN

### What is the role of prophylactic LN dissection in urethral cancer?

- no benefit

### What is the treatment of carcinoma of the bulbomembranous urethra?

- radical cystoprostatectomy, pelvic lymphadenectomy, and total penectomy → best chance for cure  
→ some may be amenable to TUR or segmental resection → rare

### What is the treatment of carcinoma of the prostatic urethra?

- superficial lesion: TURP
- others: cystoprostatectomy and total urethrectomy

### How may one distinguish b/w prostatic adenoca from poorly differentiated TCC infiltrating the stroma?

- tissue staining for PAP and PSAP: -ve in TCC, +ve in prostate  
→ -ve in 1.6% of prostate cancers
- cytokeratin stains: +ve in TCC

### What is the role of radiation for urethral cancer?

- reserved for pts w/ early-stage lesions of anterior urethra that refuse surgery  
→ may result in urethral stricture and chronic edema  
→ doesn't prevent new tumour formation

### How does one surveil pts for urethral recurrence after cystectomy for TCC?

- urethral washings for cytology, urethral palpation, and urethroscopy q3-4mo x 5 years

### Describe the technique of total urethrectomy post-cystectomy.

- modified lithotomy
- 5cm midline or inverted U-shaped perineal incision
- 16F Robinson catheter in urethra, fix end to glans
- divide subcutaneous tissue and bulbocavernosus in midline  
→ retract to expose corpus spongiosus
- mobilize sponge, dissect from cavernosa
- invert penis
- excise fossa and meatus, free distal urethra
- dissect proximal urethral bulb sharply to level of perineal membrane
- isolate and divide urethral branches of the internal pudendal artery, just inferior to perineal membrane
- Penrose drain
- close bulbocavernosus and skin

### What are the etiologies of female urethral cancer?

- chronic irritation
- UTI
- caruncle
- papillomas
- adenomas
- polyps
- leukoplakia of the urethra



## Chapter 84 Questions - Penile OR.doc

### What are the sx of urethral cancer in a female?

- urethral bleeding
- urinary frequency
- obstructive sx
- palpable urethral mass
- foul-smelling discharge and secondary infection

### What is the lymphatic drainage of the female urethra?

- anterior urethra and labia: superficial and deep inguinal nodes
- posterior urethra: external iliac, hypogastric, obturator nodes

### How advanced are urethral cancers in women at presentation?

- 1/3 of pts have clinically palpable inguinal nodes
- 20% have pelvic LN involvement
- 15% develop mets during follow-up

### What is the natural history of female urethral cancer?

- metastasizes systemically w/o regional LN involvement

### How does location of a urethral tumour in a female affect its pathology?

- proximal urethra: SCC predominant (60%), tend to be high grade and locally advanced

### How does one stage female urethral cancer?

- pelvic EUA
- cystourethroscopy
- biopsy
- CXR, CT, bone scan

### What is the treatment for female urethral cancer?

- Distal small lesions
  - local excision → tend to be superficial and well-localized
- Proximal: multimodal therapy
  - cystourethrectomy (anterior exenteration) and wide margin of vagina
    - Morash (2004): should be reserved for salvage: reasonable NED rates
  - inguinal LN dissection if palpable disease
  - chemo/rads + surgery if feasible

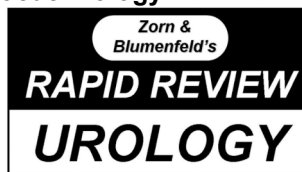
### What is the most significant prognostic factor for local control and survival of female urethral cancer?

- anatomic location and stage
  - low-stage distal better prognosis (89% 5-yr DSS, 33% for high-stage)

### What is the role of radiation in female urethral cancer?

- sufficient to control small lesion in distal urethra
  - poor 10 year survival





## **Chapter 85**

### **• Epidemiology, Etiology, and Prevention of Prostate Cancer •**

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#### **What happened to prostate cancer incidence around the time PSA became available?**

- Surveillance, Epidemiology, and End Results program of NCI (SEER database)
  - incidence increased 2.3% annually from 1975-85, 6% annually from 1985-89, then jumped to 18.4% from 1989 to 1992
  - from 1992-5, prostate cancer incidence declined at a rate of 14% annually

#### **What are the differences in annual incidence of prostate cancer based on race and nationality?**

- black men have the highest incidence of prostate cancer
- overall incidence of prostate cancer lower in Asians, Hispanics, and Natives compared to whites and blacks
- Scandinavian countries have particularly high rate of prostate ca dx and death
- Asian countries have lowest prostate cancer incidence (esp Japan and China)
  - higher in these men that move to US

#### **Why has the incidence of prostate cancer continued to rise in men in their 50s?**

- screening effect
  - new-incident prostate cancers are more likely to be diagnosed at an earlier age

#### **How has the introduction of PSA testing affected prostate cancer stage at diagnosis?**

- incidence of local-regional disease has increased
  - pathologically confined prostate cancer increased from 40-75%
- incidence of metastatic disease has decreased
  - incidence of +ve margins and SV invasion decreased from 30-14% and 18-5%
- mean age of surgical pts decreased from 65 to 62

#### **How has prostate cancer mortality changed over the past 20 years?**

- US
  - rose slowly during 70s and 80s
  - mortality rose at an annual rate of 3.1% from 1987-1991
  - decreased at a rate of 1.9% from 1991-1995
- Worldwide
  - mortality continued to rise in Netherlands
  - no change in Sweden

#### **How has prostate cancer screening affected prostate cancer mortality rate?**

- very controversial
  - stage migration from late to early stages may be due to screening
  - less clear whether screening directly due to decreasing mortality
  - screening may have led to decreased mortality rates in pts w/ tumours w/ shorter lead times (more aggressive cancers)
  - decreases in mortality may be due to aggressive treatment policies
  - prostate cancer mortality rates have not decreased in countries where PSA not routine

#### **What are the potential RF for developing prostate cancers?**

- FHx: genetics and heredity → likely AD transmission of a rare allele
  - one 1<sup>st</sup> degree relative w/ prostate ca: 2X risk
  - 2-3 1<sup>st</sup> degree relatives: 5X and 11X risk
  - relatives affected at younger age: increased risk
- androgens: not resolved
  - blacks have increased levels of circulating androgens
- genetic polymorphisms

## Chapter 85 Questions - Prostate ca epi.docdemiology

- IGF-1
  - IGF-1 has an antiapoptotic/mitogenic effect on prostate cells (normal and transformed)
  - high plasma levels correlate w/ increased risk of prostate ca
- diet
  - increased incidence of prostate ca in men immigrating from Japan and China
  - fat: high levels of dietary fat may increase risk of prostate ca
  - Ca: increased Ca intake may increase risk by downregulating vitamin D, promoting cellular proliferation
  - lycopene: potent antioxidant, may decrease risk of prostate ca, bioavailability increased by cooking
  - Se: mortality from ca lower in states w/ high soil Se
  - vit E (alpha-tocopherol): ATBC study (JNCI 1998)
    - 29133 male smokers aged 50-69 placed on vit E or  $\beta$ -carotene or placebo or both for 5-8 yrs
    - 32% decrease in prostate ca incidence and 41% decrease in prostate ca mortality w/ vit E supplements (50 IU) vs placebo
      - ◆ PSA done, no DRE
- vasectomy/sexual activity: controversial and unresolved → 2 large cohort studies showed increased risk, other have not
- smoking/EtOH
  - heavy EtOH use may increase estrogen production and decrease T
- ht/wt

### What are the possible genetic polymorphisms involved in the development of prostate cancer?

- 5 $\alpha$ -reductase type 2 gene (SRD5A2): converts T to DHT
  - longer TA allele in blacks
  - A49T allele: higher activity of T conversion → increased risk in blacks
  - V89L allele: lower conversion of T → decreased risk in Asians
- type 2 3 $\beta$ -hydroxysteroid dehydrogenase (HSD3B2)
  - initiates inactivation of DHT
- cytochrome P450C17 $\alpha$  (CYP17)
  - catalyzes 17 $\alpha$ -hydroxylase/17,20 lyase activities in T synthesis
  - 2 alleles: A1 and A2 → A1 more common in Swedish prostate cancer cohort
- cytochrome P450 3A4 (CYP3A4)
  - involved in oxidative degradation of T
  - CYP3A4-V common in white men w/ locally advanced and poorly differentiated prostate ca
- androgen receptor polymorphisms
  - CAG repeats: short repeat lengths may result in increased AR-mediated androgen activity and increased BPH and prostate ca
    - highest prevalence in blacks, lowest in Asians
  - GGN repeats: effect not known
- vitamin D receptor
  - vitamin D is a steroid that can inhibit proliferation and induce differentiation of prostate cancer cell lines
  - vitamin D can inhibit growth of prostate cancer
  - lower vitamin D plasma levels can increase risk of prostate ca
  - men w/ homozygous t allele for TaqI RFLP have 1/3 risk of prostate ca requiring RP

### Through what mechanisms is fat believed to increase the risk of prostate ca?

- fat can alter androgen levels
- fat may be a source of free radicals
- proinflammatory FA metabolites may be carcinogenic

### How many prostate cancers are inherited?

- 10%

### What genes are involved in inherited prostate cancer?

- HPC-1 (hereditary prostate cancer 1)
  - long arm of chromosome 1 (1q24-25): pts develop prostate ca at an early age
- PCAP and CAPB
  - 1q42: PCAP → early-onset disease
  - 1p36: CAPB → associated w/ prostate and brain cancers
- HPCX (hereditary prostate cancer X)
  - X-linked mode of prostate ca inheritance: 16% of inherited prostate ca
  - more common in men w/ affected brothers than in men w/ affected fathers

## Chapter 85 Questions - Prostate ca epi.docdemiology

→ Xq27-28

### What genes are involved in the development of sporadic prostate ca?

- LOH at chromosome 8p
  - tumour suppressor site
- Nkx3.1
  - androgen regulated and prostate-specific gene on 8p21
  - belongs to family of homeobox genes

### What genetic alterations are involved in prostate cancer progression?

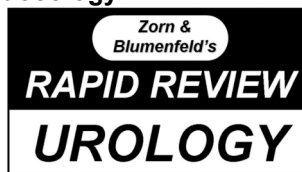
- normal prostate → histologic prostate ca
  - germ line mutations: HPC1, HPCX
  - genetic polymorphisms: VDR, SRD5A2
  - AR polymorphisms: CAG repeat lengths
  - expression of telomerase: reverse transcriptase that prevents telomere shortening, allowing cell renewal
  - loss of GSTP1 expression
    - glutathione-S-transferase enzymes (like GST-pi) normally protect against free radicals → absent in PIN and prostate ca
  - LOH at 8p
  - IGF
- histologic prostate ca → invasive localized prostate ca
  - increased metalloproteinase expression
    - degrades cellular matrix and promotes angiogenesis
  - increased VEGF expression
    - proangiogenic genes
- invasive localized prostate ca → metastatic prostate ca
  - PTEN inactivation: LOH at 10q (tumour suppressor gene)
    - PTEN/MMAC tumour suppressor gene at 10q23 → mutated in large # of human cancers
    - PTEN is a negative regulator of the PI3 kinase/Akt signaling pathway (dephosphorylates and inactivates PI3 kinase)
      - ◆ activation of PI3 kinase leads to Akt activation (an oncogene) leading to prolif/inhib of apoptosis
  - loss of p27 (tumour suppressor gene on 12p12)
    - association b/w loss of p27 and increased risk of biochemical recurrence
    - normally regulates progression of cell cycle from G1 to S phase by binding to cyclin E/cdk2 complex
    - loss of p27 allows cells to progress through cell cycle
  - loss of E-cadherin
    - family of adhesion proteins: reduced in significant percentage of prostate cancers, esp if poorly differentiated
  - MYC amplification
    - gain of long arm of chromosome 8q
    - MYC oncogene on 8q24 → amplified and overexpressed in many locally advanced and metastatic tumours
    - predicts for systemic progression and death from prostate cancer
- metastatic prostate ca → androgen resistant prostate ca
  - AR mutation and amplification
    - converts AR antagonists (bicalutamide) into AR agonists
  - Bcl-2 expression
    - oncogene that prevents apoptosis
    - expressed in large # of prostate tumours

### What are the potential strategies to prevent prostate ca?

- Screening for high-risk individuals
  - IGF-1 levels
  - genetic polymorphisms
- Dietary intervention
  - fat
  - soy: genistein inhibits prostate cancer
  - lycopenes
  - Se
  - vitamin E
  - green tea
- Chemoprevention

### **Chapter 85 Questions - Prostate ca epi.docdemiology**

- antiandrogens: PCPT (finasteride)
- retinoic acids (vitamin A)
- vitamin D analogues
- DFMO
  - inhibits ornithine decarboxylase, the rate-limiting enzyme in polyamine synthesis
  - polyamines present in prostate → may cause prostate epithelial differentiation and proliferation



## **Chapter 86**

### **• Pathology of Prostatic Neoplasia •**

---

#### **What is PIN?**

- prostatic intraepithelial neoplasia
  - architecturally benign prostatic acini or ducts lined by cytologically atypical cells

#### **How is PIN graded?**

- Low-grade PIN
  - PIN1: mild dysplasia
- High-grade PIN: ++ interobserver variability b/w PIN2 and PIN3, same risk of ca on 2<sup>nd</sup> bx
  - PIN2: moderate dysplasia
  - PIN3: severe dysplasia

#### **Why is low-grade PIN not commented on in diagnostic reports?**

- pathologists cannot reproducibly distinguish b/w low-grade PIN and benign prostate
- no increased risk of developing ca on repeat bx

#### **Where is PIN often found in the prostate?**

- increase in high-grade PIN in peripheral zone: incidence 1-16.5% on TRUS/bx (mean **6%**)

#### **What different types of patterns of PIN exist?**

- tufting: tufts or bumps
- micropapillary: projections
- cribriform: punched out holes
- flat

#### **What is the significance of high-grade PIN being found in a needle bx of the prostate?**

- 23-35% risk of cancer on repeat bx: if high-grade PIN found, repeat biopsy performed → **takes 10y to develop to ca**
  - PIN found on TURP may also increase risk of prostate ca: biopsy, esp younger men
- is a precursor to many peripheral intermediate- to high-grade adenocarcinomas of the prostate
  - if 2 repeat biopsies –ve, cancer unlikely
  - **PIN does not cause increased PSA**

#### **What is the natural hx of PIN?**

- unknown: no way to monitor a focus of PIN

#### **Where is prostatic adenocarcinoma usually located?**

- in T2 and 85% of T1c tumours, major tumour mass is peripheral
  - rest are in TZ
- multifocal in 85%
  - T2a-T2b lesions on DRE are T2c on path in 70%
- if feels unilateral on DRE, 70% chance bilateral on pathologic specimen

#### **Where does EPE usually occur?**

- usually posteriorly and posterolaterally

#### **What is the significance of perineural invasion on RP specimens?**

- does not worsen prognosis: is along a plane of decreased resistance

#### **How can prostate cancer spread to the seminal vesicles?**

- tumour penetration of the prostatic capsule at the base of the gland: most common
  - growth and extension into peri-SV soft tissue and eventually into SV proper

## Chapter 86 Questions - Prostate ca path.docology

- direct extension through ED into SV
- direct extension from base of prostate into SV wall
- mets to SV: least common

### Where are the most frequent sites of metastatic prostate ca?

- LN, bone: most common → L supradiaphragmatic LN
- lung, bladder, liver, adrenal, testis

### How does tumour volume relate to grade?

- tumour volume is proportional to grade
- TZ tumours extend out of prostate at larger volumes than PZ tumours: due to lower grade and greater distance from gland edge

### How does one grade prostate cancer?

- Gleason system
  - based on glandular pattern of tumour at low magnification
  - cytologic features play no role
  - primary and secondary architectural patterns are identified + given grade of 1-5, added to get *Gleason score* or *Gleason sum*
- Gleason 1: relatively circumscribed nodules of uniform, single, separate, closely packed, medium-sized glands
- Gleason 2: similar to pattern 1, slightly looser pattern
  - may see crystalloids in glands: also present in Gleason 3 pattern
- Gleason 3: infiltrates nonneoplastic prostate
  - glands have marked variation in size and shape, w/ smaller glands than pattern 1 or 2
  - may see smoothly circumscribed smaller cribriform glands
  - 3 patterns
    - angulated single separate glands
    - cribriforming
    - tiny single separate glands
- Gleason 4: glands are no longer single and separate
  - may see large irregular cribriform glands
  - **significantly worse prognosis compared to pure Gleason 3**
  - 3+4 better prognosis than 4+3
  - 2 patterns
    - large masses of fused cells: irregular
    - hypernephroid pattern: cords of bland looking cells, looks like clear cell RCC
- Gleason 5: no glandular differentiation, made of solid sheets, cords, single cells, or solid nests of tumour w/ central comedonecrosis, or signet rings (solitary nucleus w/ large vacuole)
  - 2 patterns
    - fused: no lumens
    - comedonecrosis

### What features may distinguish prostate cancer from normal glands?

- nucleoli
- basal layer
- infiltrative pattern
- cytoplasm darker (more eosinophilic): different staining quality

### Why are prostate biopsies never graded Gleason scores of 2-4?

- most tumours w/ combined score 2-4 are graded as a score of 5-6 on expert review
- poor reproducibility in dx of score 2-4 even among experts
- score 2-4 may adversely affect pt care: MDs may feel they do not require therapy

### What ancillary techniques can one use to diagnose prostate adenocarcinoma on needle biopsy?

- use Ab to HMW cytokeratin
  - benign glands contain basal cells and are labelled w/ these Ab
  - prostate cancer shows no staining

### What is ASAP?

- atypical small acinar proliferation: incidence of 0.4%-23.4%



## Chapter 86 Questions - Prostate ca path.docology

- atypical glands: high chance of infiltrating cancer
- must send initial biopsy for path review or try to resolve bx w/ ancillary techniques
- all pts w/ atypical diagnosis on needle bx should get repeat biopsy
- **likelihood of cancer is 42-49% (higher than PIN!)**

### How do findings on needle bx correlate w/ RP specimens?

- adverse findings on needle bx accurately predict adverse findings in RP specimen (Gleason 7 in bx: 88% same in RP)
- favourable findings on needle bx do not necessarily predict favourable findings in the RP specimen (Gleason 5-6 bx: 64% in RP)
- if PNI seen on needle bx, associated w/ increased risk of EPE in RP specimen and +ve LN

### How does Gleason grade on biopsy correlate w/ prognosis?

- if score 8-10 on biopsy and LN involved, these men will not benefit from RP
  - if LN +ve at time of RP, RP should be aborted
  - if LN -ve, cure after RP is possible

### How does SV or LN involvement affect prognosis?

- 25% of pts w/ SV invasion and 0% w/ LN mets are biochemically progression free at 10y after RP
- SV invasion associated w/ markedly adverse prognosis

### What is the meaning of "adenosis" on a TURP specimen?

- atypical adenomatous hyperplasia
  - multifocal lesion found in TZ: 1.6% of TURPs, 0.8% of TRUS/bx
  - most common lesion confused w/ low-grade prostate adenoca
  - no increased risk of prostate ca

### What is the prognosis of men w/ +ve margins after RP?

- 50% of men w/ +ve margins progress post-RP

### What are the independent predictors of progression after RP?

- Gleason grade
- ECE
- +ve margins
- LN status

### How does tumour volume affect prognosis?

- does not independently predict post-RP progression outside of grade and pT stage

### How does combination endocrine therapy affect the prostate and its grading?

- causes atrophic changes w/ immature squamous metaplasia
- grade often appears artefactually higher
- cannot be assigned an accurate Gleason grade if pronounced hormone effect

### What are the various subtypes of prostate cancer and how do they behave?

- NeEdLe The MASSSS
- Neuroendocrine
- Endometrial/ductal
  - most are advanced at presentation and are aggressive
  - may grow as an exophytic lesion into the urethra around veru
    - can cause obstruction or hematuria
- Leukemia/lymphoma
- TCC
- Mucinous: least common variant
  - aggressive, high chance of bone mets
- Met
- Small-cell
  - most lack hormone production, but are the majority of ACTH/ADH producing prostatic tumours
  - average survival < 1year
- Signet ring cell carcinoma
  - rare tumour

## Chapter 86 Questions - Prostate ca path.docology

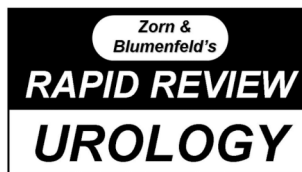
- > 25% of tumour composed of signet ring cells (clear cytoplasm displacing nucleus)
- acts like Gleason 10: aggressive
- SCC of the prostate
  - usually advanced disease at time of presentation
  - PSA may be normal
  - rare to have paraneoplastic syndromes
  - poor survival, bony mets
- Sarcoma/mesenchymal tumours
  - sarcomas: 0.1-0.2% of all malignant prostate tumours
    - rhabdomyosarcoma: most common, seen almost exclusively in childhood
    - leiomyosarcoma: most common in adults
    - carcinosarcomas

### What subtype of prostatic sarcoma resembles a tumour seen in the breast?

- phyllodes tumour of the prostate
  - mesenchymal tumour of the prostate arising from prostatic stroma

### What is the natural hx of UCC of the prostate?

- propensity to invade the BN and surrounding tissues: >50% present w/ T3-T4 disease
- 35-45% of cystoprostatectomies performed for UCC contain prostatic involvement
- 20% present w/ distant mets to bone, lung, liver
  - osteolytic bone mets
- involves prostatic ducts and acini in pts w/ hx of bladder CIS that have been tx w/ BCG
- may see direct invasion from bladder UCC into prostatic stroma
  - difficult to differentiate b/w UCC and prostatic adenoca: stain for PSA, PSAP, HMW cytokeratin (34βE12)
  - 34βE12 +ve in 57-70% of UCC, -ve in prostate cancer, +ve in normal prostate



## Chapter 87

### • Ultrasonography and Biopsy of the Prostate •

---

#### **What are the indications for TRUS/bx of the prostate?**

- men w/ life expectancy > 10 yrs w/ abnormal DRE or increased PSA

#### **How does the TRUS convert signals to images?**

- transducer sends out sound waves and collects echoes that return at different rates depending on tissue properties
- acoustic-electric conversion: sonographic signals transformed to electrical impulses and displayed as pixels in varying shades of gray

#### **What is the typical frequency and focal range of a TRUS transducer?**

- 7 MHz (ranging from 4-8MHz)
  - 7 MHz: high res image w/ range of 1-4cm from transducer
  - 4 MHz: focal range 2-8cm, at lower resolution

#### **What is the role of colour Doppler in detection of prostate cancer?**

- increased Doppler signals may be present in prostate cancer
  - also in inflammation and BPH: not specific

#### **What is involved in the pre-operative preparation for TRUS/bx?**

- History
  - PMHx: implants, valve disease, allergies
  - sx of acute prostatitis
  - UTIs
  - medications: take normal BP/cardiac meds
  - d/c Coumadin, NSAIDs and ASA x 10d prior
- Antibiotic prophylaxis
  - quinolone prior to procedure
  - implants/valvular heart disease: amp/gent IM
- Bowel prep: enema
- Anaesthesia: lidocaine jelly +/- periprostatic nerve blockade

#### **How does one perform TRUS?**

- positioning
  - LLD position, knees/hips at 90 degrees
  - buttocks flush w/ table
- TRUS performed in both transverse and sagittal planes
- volume determination
  - volume in cc ~ weight in grams
  - $\text{volume} = 8 \times \text{surface area}^2 \div 3\pi \times \text{transverse dimension} \sim \pi \div 6 \times \text{transverse} \times \text{AP} \times \text{longitudinal dimension}$

#### **What is meant by the term *time-gain compensation*?**

- automatic gradual amplification by the US of echoes that grow more faint w/ increasing distance from the transducer
  - aka sensitivity time control, near gain suppression

#### **What are the complications of TRUS/bx?**

- infection
  - bacterial sepsis
    - rate of bacteriuria: 20-53%, bacteremia: 16-73%
    - usually due to *E. Coli*, *Enterococcus*, *Klebsiella*, *Bacteroides*, *Clostridium*
- bleeding: > 50% of pts have hematuria for up to 7days after
  - hematuria, hematochezia, hematospermia

## Chapter 87 Questions - TRUS-bx.doc

- amount of bleeding associated w/ total # of biopsies
- urinary retention: 1-2% → usually resolves
  - increased risk if high AUA sx score
- vasovagal reaction: 8%
  - vagal nerve stimulation by anxiety and pain: vasodilation and decreased perfusion
  - place pt in Trendelenberg, give IV fluids if needed, PO glucose/candy

### Describe the zonal anatomy of the prostate on TRUS.

- central zone
- peripheral zone
- transitional zone
  - boundary b/w TZ and PZ (surgical capsule) is hypoechoic convex line
  - w/ increasing BPH, boundary is less convex
  - BN and preprostatic sphincter located b/w lobes of TZ
    - appear as inverted Y (Eiffel Tower sign) in axial plane, or as curved funnel shape in sagittal plane

### What are the different types of sonographic artefacts that can occur w/ TRUS?

- shadowing: due to calcification or air
- increased through enhancement: due to fluid
- reverberation artefact
  - due to sound waves striking very echogenic surface: signal ricocheted back and forth b/w transducer and reflector
- phase cancellation artefact
  - occurs w/ signal tangentially strikes curved structure, reflecting it laterally: appears as blank space
- lateral and anterior refraction aka dispersion or scatter
  - spread of sound waves in fanlike configuration
- rectal pseudomasses
  - due to rectal folds or stool

### What is the appearance of prostate ca on TRUS?

- 70% of palpable nodules are hypoechoic
- 50% of nonpalpable cancers are hypoechoic
- 80% of TZ malignancies are isoechoic
  - not very specific: caused also by inflammation, atrophy, hyperplasia, and normal prostate

### What is the appearance of prostate ca on TRUS after radiation?

- External beam
  - volume of prostate decreased by 6mo
  - diffusely hypoechoic prostate
  - poor intraprostatic anatomy
  - thickened rectal surface
- Brachytherapy
  - same as external
  - increase in volume for 1<sup>st</sup> few weeks due to postimplantation edema
  - seeds visible

### What is the appearance of prostate ca on TRUS after hormones?

- 30% volume decrease w/ androgen deprivation (10-60%)

### What is the normal appearance of TRUS after RP?

- smooth tapering of BN to urethra
  - blunted nontapered appearance of anast associated w/ postoperative UI
- nodule of tissue anterior to anastomosis = ligated dorsal venous complex

### What is the appearance of the following lesions on TRUS:

- Prostatic UCC
  - invasion of prostatic urethra generally not visible
  - 71% of prostatic stromal invasion shows hypoechogenicity
- SCC
  - irregular anterior mass w/ hyperechogenicity
- Adenoid cystic carcinoma

## Chapter 87 Questions - TRUS-bx.doc

- numerous cysts: multiple evenly distributed cysts w/ increased through transmission
- Sarcomas
  - RMS: similar to normal prostate
  - radiation induced sarcoma: irregular hypoechoic mass w/ anechoic area consistent w/ necrosis
  - cystosarcoma phyllodes: large irregular mass w/ multiple large anechoic cysts of variable size
- Lymphoma
  - not visible

### What are the various techniques of TRUS/bx pattern?

- blind biopsy: digitally directed
- directed biopsy: from suspicious lesion seen on TRUS
- sextant biopsy: midlobe parasagittal plane at apex, midgland, and base bilaterally → may do lateral 1/3 rather than midlobe
  - all pts: sens 66-85%
  - normal DRE: sens 60%, spec 100%
  - ca > 2cm or PZ cancers: sens 83% or 71%
  - TZ cancer: sens 33%
- anterior biopsy
  - useful to hit TZ, an area not well sampled by sextant biopsy
  - useful for pts undergoing repeat biopsy after prior -ve sextant biopsy
  - perform near midline, close as possible to urethra and AFMS – 2 cores from each lobe of TZ
- lateral biopsy
  - PZ wraps anteriorly around TZ – slightly improved sensitivity
- extended field/saturation biopsy
  - improved cancer detection
- repeat bx
  - **should include sextant + additional TZ or lateral biopsies (extended field)**
  - cancer detection on 3<sup>rd</sup> bx set: 30%
- transperineal (TPUS): for pts w/o rectum

### Where does one aim the TRUS probe to perform sextant biopsies?

- midlobe parasagittal plane at apex, midgland, and base bilaterally

### What are the indications for repeat biopsy?

- in pts in whom initial set of biopsies -ve, but suspicion is high
  - very high PSA
  - rapidly rising PSA
  - blacks
  - FHx
  - PIN on initial bx

### What is the appearance of ECE on TRUS?

- TRUS sensitivity of < 60% for ECE, and cannot detect microscopic ECE
- irregular capsular bulge or frank extension of hypoechoic lesion into periprostatic fat
- loss of triangle formed in sagittal plane by prostatic apex, urethra, and rectal wall (trapezoid area)

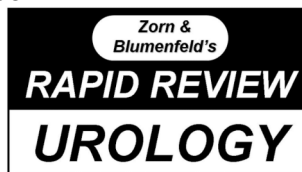
### How does perineural invasion on TRUS/bx affect RP technique?

- indication for resection of NVB on side of involvement

### What is the appearance of SV involvement on TRUS?

- appear abnormal in 90% of cases
  - loss of normal "beak" configuration: angled, tapering junction b/w SVs and base of prostate in sagittal plane
  - hyperechogenicity and enlargement of SV
- asymmetry: very common, not significant





## **Chapter 88**

### **• Diagnosis and Staging of Prostate Cancer •**

---

#### **What are the sx of prostate cancer?**

- rare to have sx until advanced disease
  - low proportion of pts w/ prostate cancer detected from sx of advanced disease
- obstructive or irritative sx
  - due to growth of prostate ca into urethra or BN
- hematospermia
- ED: if involves pelvic plexus
- metastatic sx
  - bone pain
  - anemia
  - lower extremity edema
  - malignant retroperitoneal fibrosis
  - paraneoplastic syndromes from ectopic hormone production
  - DIC

#### **What is the most useful 1<sup>st</sup>-line test for assessing the risk of prostate cancer?**

- combination of DRE and PSA

#### **What is the family of tumour markers that includes PSA?**

- kallikrein tumour markers: 3 known and related proteins
  - tissue or pancreatic/renal kallikrein (hK1)
    - 60% a.a. sequence homology w/ PSA
    - expressed in prostate, kidney, pancreas, salivary glands
  - glandular kallikrein (hK2)
    - 78% a.a. sequence homology w/ PSA
    - expressed in prostate almost exclusively, although at lower levels than PSA
    - plays a role in regulating PSA activity: cleaves pro-PSA into PSA
  - PSA (hK3)

#### **What is the function of PSA?**

- involved in liquefaction of the seminal coagulum

#### **What proteins bind PSA?**

- most PSA in sera (65%-90%) bound or complexed to antiproteases ACT ( $\alpha_1$ -antichymotrypsin) or MG ( $\alpha_2$ -macroglobulin)
  - PSA-ACT immunodetectable and inactive
  - PSA-MG undetectable and partially active
- 10-35% of PSA is free (unbound), detectable, and inactive

#### **How is PSA cleared?**

- bound PSA: through liver
  - size of complexed PSA too big for glomerular filtration
- free PSA: glomerular filtration or formation of new complexes w/ antiproteases

#### **What is the t<sub>1/2</sub> of PSA?**

- 2-3 days → takes several weeks after RP for PSA to become undetectable

#### **What factors affect serum PSA level?**

- androgens

## Chapter 88 Questions - Prostate ca dx.doc

- PSA detected within the prostate during 2 peaks: 0-6 months, and after 10yrs (at puberty) → correlates w/ T levels
- race
  - blacks w/o prostate ca have higher PSA values than whites
- age
- prostate volume
  - PSA increases 4% per cc of prostate volume
- meds: finasteride
- prostate disease or manipulation

### What are the AUA Guidelines for PSA testing?

- Diagnosis
  - Indications
    - men > 50 w/ life expectancy > 10yrs
    - men at higher risk (blacks, FHx): start at age 40
  - inform pts of risks and benefits
  - Hx/Px
    - DRE
      - wait 3-4 weeks for PSA testing after cysto or TRUS/bx
  - TRUS/bx: if PSA > 4, significant PSA rise, or abnormal DRE
  - bone scan: only if PSA > 20, significant sx, Gleason 8-10, or T3 disease (even if PSA < 10)
  - CT/MR: if PSA > 25
  - PLND: needed if PSA > 20 + Gleason 4-6, or if PSA > 10 and Gleason 7-10
- Post-tx management
  - offer periodic PSA to detect recurrence
    - detectable PSA = recurrence → salvage rads, hormones, cryo

### What is the average yearly increase in PSA for men?

- men w/o BPH: 0.04 ng/mL per year
- men w/ BPH: 0.07-0.27 ng/mL per year

### What are the potential causes for a PSA elevation?

- prostate disease: BPH, prostatitis, prostate cancer → most important
- prostate manipulation: prostate massage, biopsy, DRE, ejaculation

### How does ejaculation affect PSA levels?

- no significant change in men aged 30-40
- significant increase in men > 50
  - repeat after 48hrs → should return to baseline

### How does DRE affect PSA levels?

- can increase PSA, but is not clinically significant: is within lab error of assay

### How does finasteride affect PSA levels?

- lowers PSA level by 50% **after 12mo of treatment**
- if one is to start pt on finasteride, must get baseline PSA before initiation of tx and follow w/ serial PSA values
  - if PSA does not decrease by 50% or there is an increase in PSA, suspect occult prostate ca
- **finasteride does not affect PSA free-to-total ratio** (Keetch 1997)

### How does routine use of PSA affect diagnosis of prostate cancer?

- PSA increases detection of prostate ca over use of DRE
- PSA improves predictive value of DRE for ca
- PSA increases detection of prostate cancers that are organ confined
- PSA is the single test w/ highest PPV for ca

### What are the chances of having prostate cancer on biopsy w/ PSA of the following levels:

- PSA < 4: 2%
- PSA > 4: 33%
- PSA 4-10: 25%
- PSA >10: 50-66%



## Chapter 88 Questions - Prostate ca dx.doc

- PSA > 20: pelvic LN involvement in 20%
- PSA > 50: pelvic LN involvement in 75%

### Why is the use of PSA without DRE not recommended?

- 25% of men w/ prostate cancer have PSA < 4
  - Catalona 1997 JAMA: prostate cancer in 22% of 332 men w/ PSA 2.6-4 and normal DRE that underwent bx
    - all cancers clinically localized, 81% pathologically localized (70% confined if PSA > 4)
    - free PSA cutoff of < 27% for performing biopsy would have detected 90% of cancers, avoided 18% of benign biopsies, and yielded a PPV of 24% in men who underwent biopsy

### How does PSA affect lead time in prostate cancer diagnosis?

- increases lead time by 4 years (BLSA 1997)

### What is the evidence that shows that PSA + DRE (vs. DRE alone) leads to detection of more pathologically confined cancers?

- Catalona 1994: PSA cutoff of 4 + abnormal DRE → pathologically organ confined disease in 71%
  - **majority of cancers detected by DRE + PSA are organ confined**
    - 6630 men underwent DRE + PSA, + quadrant biopsies if PSA > 4 or +ve DRE
    - PSA detected more tumors (82%) than DRE (55%)
    - PSA + DRE in combination increased detection of organ confined disease by 78% over DRE alone
- Chodak 1989: DRE alone as screen for prostate ca → organ-confined disease in < 50%
  - **majority of cancers detected by DRE alone are advanced**
    - 2131 men > 45yrs w/ DRE: biopsy recommended if induration, asymmetry or nodules
    - biopsy performed on 144 men, 36 malignant tumors were detected, of which 68% clinically localized
    - surgical staging upstaged 50 per cent of pts w/ clinical stage B disease to stage C or D1 disease

### What are the pros and cons of use of PSA + DRE?

- Pros
  - facilitates early detection
  - cancers found are amenable to curative treatment
  - specificity improved w/ use of isoforms: complexed PSA, free PSA, PSA velocity/density
  - mortality rates dropping
- Cons
  - serum PSA does not correlate w/ prostate cancer volume
  - impact on decreased mortality not known
  - over-detection a growing problem
  - treatment associated w/ side effects

### What methods are available to improve specificity of PSA to only men with prostate cancer?

- age- and race-adjusted PSA
- PSA density
- PSA transition zone volume
- PSA velocity/doubling time
- free-to-total ratio of PSA
- pro-PSA
- complexed PSA

### What are the age- and race-specific PSA ranges to detect prostate cancer based on 95% specificity?

- |                |                 |                   |
|----------------|-----------------|-------------------|
| • White males  | • Black males   | (Oesterling 1993) |
| → 40-50: 0-2.5 | → 40-50: 0-2.4  |                   |
| → 50-60: 0-3.5 | → 50-60: 0-6.5  |                   |
| → 60-70: 0-4.5 | → 60-70: 0-11.3 |                   |
| → 70-80: 0-6.5 | → 70-80: 0-12.5 |                   |

### How does one calculate PSA density?

- PSA / US determined prostate size
  - PSA density > 0.15 proposed as a threshold for recommending prostate biopsy in men w/ PSA 4-10 and normal DRE/TRUS
  - usefulness not confirmed in all studies: higher PSA densities in pts w/ prostate cancer size may be due to smaller target to hit w/ biopsy gun, w/ higher likelihood of hitting the cancer
- PSA-TZ volume: investigational

## Chapter 88 Questions - Prostate ca dx.doc

→ BPH represents enlargement of the TZ, and PSA-TZ may help distinguish b/w BPH and cancer

### What PSA velocity is felt to be a specific marker for the presence of prostate cancer?

- PSA rate of change > 0.75 ng/mL per year (Carter, Catalona)
- D'Amico (NEJM 2004): preop PSA velocity and risk of death from prostate cancer after RP
  - 1804 men in prospective screening for prostate cancer from 1989-2002 → 1095 pts w/ localized prostate cancer
    - all pts had DRE, PSA, and TRUS/bx
  - PSA velocity > 2 ng/mL/year (by linear regression): shorter time to death from prostate cancer or from any cause
    - increasing PSA at dx, T2 disease, and Gleason 8-10 also predicted death from prostate cancer
  - ECE (T3) in 25%, +ve margins in 25%, almost all LN -ve
- useful only if measured over at least 18 months and > 3 measurements: short term changes due to physiologic variation
- cannot use if PSA < 4
- Catalona (1994): used cutoff of 0.75 if initial PSA < 4.0, cutoff of 0.40 if initial PSA > 4
- Stamey: PSA < 10 in men mostly from BPH, not from cancer

### What is the utility of the PSA doubling time?

- PSA doubling time < 3 yrs may predict for rapid progression
  - median PSA<sub>dt</sub> 7 years (42% > 10 yrs, 22% < 3 yrs)
  - Klotz: subtracted PSA (remove component of PSA due to BPH): will decrease doubling time
    - PSA DT cutoff of 3 years captures 22% of pts
    - subtracted PSA: only 1.2 years to get same proportion of pts: 25% w/ rapid progression
- for pts w/ PSA 6-8, PSA DT 3 yrs = 1 yr rise of about 2 ng/ml

### Who gets salvage rads for recurrent prostate cancer after RP?

- PSA doubling time identifies pts that will respond to salvage radiation
- Stephenson (JAMA 2004): salvage rads for recurrent prostate cancer after RP
  - 500 pts received rads for detectable/increasing PSA after RP
  - 50% experienced disease recurrence after rads, 10% had distant mets, 4% died from prostate cancer
    - 45% progression-free at 4 years
  - **predictors of progression: Gleason 8-10, PSA DT > 10mo, +ve margins, PSA < 2, SV involvement**
    - PSA-DT < 10mo: 22% 4 yr progression free survival
    - PSA-DT > 10mo: 77%
    - if PSA > 2 after rads, is too late
- salvage rads to pts w/ PSA-DT > 10-12mo, +ve margins
- if PSA-DT < 10mo, -ve margins: go straight to androgen deprivation
  - if PSA-DT < 7mo, low-likelihood of response to 2<sup>nd</sup> line hormones → straight to early chemotherapy

### How does prostate cancer affect PSA free-to-total ratio?

- **men w/ prostate cancer have more PSA bound to ACT (less free PSA)**
- difference in free-to-total ratio is greatest when comparing men w/ BPH and no cancer vs. men w/ ca and no BPH
- greatest overlap when comparing men w/ BPH and no cancer vs. men w/ cancer and BPH
- PSA cutoff of 0.18 significantly improves ability to distinguish b/w cancer and non-cancer
- Catalona 1998: 0.25 cutoff w/ PSA 4-10 → sensitivity 95%, avoids 20% of unnecessary bx
  - free-to-total ratio > 0.25: risk prostate cancer 8%
  - free-to-total ratio < 0.10: risk prostate cancer 56%

### How good is the complexed PSA as a screening tool?

- total PSA vs. complexed: no significant improvements, may identify a few additional cases
- Tyrol study: total PSA same as complexed PSA in a screened setting

### What is the PPV of suspicious DRE for prostate cancer?

- |                    |                    |
|--------------------|--------------------|
| • White males      | • Black males      |
| → PSA 0-1: 5%      | → PSA 0-1: 8%      |
| → PSA 1.1-2.5: 14% | → PSA 1.1-2.5: 37% |
| → PSA 2.6-4.0: 29% | → PSA 2.6-4.0: 50% |

### Why is TRUS alone a poor test to detect prostate cancer?

- 18% of suspicious nodules on TRUS actually contained cancer → **most lesions are not cancer**
- 37-65% of cancers not detectable on TRUS → **50% of cancers invisible on TRUS**

## Chapter 88 Questions - Prostate ca dx.doc

### What are the guidelines for screening for prostate cancer?

- detection in asymptomatic men should start at age 50
- target in men w/ > 10yr life expectancy
- higher risk: start at age 40-45
  - blacks, FHx prostate cancer in 1<sup>st</sup> degree relative

### Describe the staging system of prostate cancer.

- 2002 AJCC staging
  - T2: now back to old 1992 system: T2a < ½ of 1 lobe, T2b > ½ of 1 lobe, T2c > 1 lobe
  - T3:
    - T3a: ECE
    - T3b: SV invasion
- 1997 AJCC UICC staging system
  - Local tumour
    - TX: primary tumour cannot be assessed
    - T0: no evidence of primary tumour
    - T1: nonpalpable tumour, not evident by imaging
      - ◆ T1a: tumour found on TURP: <5% volume and Gleason grade ≤7
      - ◆ T1b: tumour found on TURP: >5% volume or Gleason grade >7
      - ◆ T1c: tumour found during TRUS/bx due to PSA increases
    - T2: palpable tumour confined to the prostate, or nonpalpable lesion seen during TRUS/bx done for increased PSA
      - ◆ T2a: tumour involves 1 lobe or less
      - ◆ T2b: tumour involves > 1 lobe
        - old 1992 system: T2a < ½ of 1 lobe, T2b > ½ of 1 lobe, T2c > 1 lobe
    - T3: palpable tumour beyond prostate
      - ◆ T3a: unilateral ECE
      - ◆ T3b: bilateral ECE
      - ◆ T3c: SV invasion
    - T4: tumour fixed or invades adjacent structures (not SV)
      - ◆ T4a: tumour invades BN, external sphincter, rectum
      - ◆ T4b: tumour invades levator, pelvic sidewall
  - Nodes
    - NX: regional LN cannot be assessed
    - N0: no evidence of LN mets
    - N1: mets in single LN <2cm
    - N2: mets in single or multiple LN < 5cm
    - N3: mets in single or multiple LN > 5cm
  - Mets
    - MX: distant mets cannot be assessed
    - M0: no evidence of distant mets
    - M1: distant mets
      - ◆ M1a: mets to nonregional LN
      - ◆ M1b: bony involvement
      - ◆ M1c: other distant sites
- Whitmore-Jewett
  - A: nonpalpable tumour (T1)
    - A1: tumour found at TUR, <5% volume, Gleason ≤7 (T1a)
    - A2: tumour found at TUR, >5% volume, Gleason >7 (T1b)
  - B: palpable tumour, confined to the prostate (T2)
    - B1: one lobe (T2a-b)
    - B1N: tumour involves ½ of lobe surrounded by normal tissue on all sides
    - B2: both lobes (T2c)
  - C: palpable tumour beyond prostate (T3-4)
    - C1: ECE or SV invasion (T3)
    - C2: tumour invades adjacent structures (T4)
  - D: LN mets or distant spread (N-M)
    - D0: elevated PAP
    - D1: regional LN mets (N+)
    - D2: distant mets (M+)
    - D3: hormone refractory disease

## Chapter 88 Questions - Prostate ca dx.doc

### What are the most important pathologic criteria that predict prognosis after RP?

- Gleason grade
- margin status
- ECE
- SV invasion
- involvement of pelvic LN

### What methods are currently available in staging prostate cancer?

- DRE: significant understaging by DRE alone → sensitivity of 52% and specificity of 81%
- serum tumour markers
  - PAP: not prostate-specific, but is directly related to tumour stage
  - PSA
- biopsy tumour grade: higher grades tend to have higher stage
- combined clinical data
  - Partin and Kattan nomograms
- imaging
  - bone scan and skeletal survey: need >50% replacement by tumour before Xray sees lesion
  - IVP: not recommended → use only if hematuria to r/o upper tract pathology
  - CT/MRI: low sensitivity, not useful routinely
    - may be useful in men w/ PSA > 20 or poorly differentiated ca on biopsy (Gleason 8-10): look for LN mets
  - TRUS
- surgery: pelvic LN dissection → 5-10% of men w/ clinically localized prostate cancer have regional LN mets
- molecular staging
  - RT-PCR identifies mRNA of PSA or PSMA from circulating prostate cells
- monoclonal Ab nuclear scanning
  - ProstaScint scan

### What can increase serum PAP?

- prostate manipulation
- prostate disease
- other malignancies
- renal, skeletal, and liver disease

### What is the contribution of BPH to overall serum PSA?

- 0.3 ng/mL per gram of BPH tissue (0.15 if monoclonal assay)

### What is the clinical utility of bone scan in men w/ prostate cancer?

- > 50% of bone density must be replaced by tumour to be seen on standard Xray
- probability of +ve scan low in men w/ PSA < 10 and no bone pain

### What are the indications for PLND during RP?

- enlarged pelvic LN on pelvic imaging
- PSA > 20
- Gleason 8-10
- palpably locally advanced tumour

### How does the ProstaScint scan work?

- monoclonal Ab to PSMA (7E11) → prostate specific membrane antigen
  - PSMA Ag expressed to a greater degree in prostate cancer cells than in normal prostate tissue
- Ab chelated to indium 111 (In 111 capromab pendetide)
- identifies microscopic cancer deposits in regional and distant sites: sensitivity 62%, specificity 72%

### What are the definitions of low-, intermediate-, and high-risk prostate cancer?

- low: PSA < 10, Gleason < 7, and T-stage T1/T2a
- intermediate: 10-20, Gleason 7, or T2b
- high: PSA > 20, Gleason 8-10, or T2c/T3-T4

### What are the treatment options for low-risk prostate cancer?

- active monitoring

## **Chapter 88 Questions - Prostate ca dx.doc**

- surgery: RP
- rads
  - external beam
  - brachy
  - cryo

### **Why is WW difficult to choose?**

- difficult to accept doing nothing
- men accept small chance for gain
- creates family conflict
- psychological upset as PSA increases





## Chapter 89

### • Radical Prostatectomy •

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#### **What is the proof that prostate cancers detected w/ DRE and PSA are clinically important?**

- Ohori (1994 JUrol): T1c/T2 prostate cancers vs. incidental prostate cancers on cystoprostatectomy specimens for bladder cancer
  - 78% of cystoprostatectomy prostates considered indolent, none had advanced pathologic features
  - advanced pathologic features in 23% T1c, 40% T2, only 9-10% indolent in each

#### **What are the important papers that describe natural hx of prostate cancer detected clinically?**

- Chodak (1994 NEJM): natural hx of conservatively tx prostate cancer
  - meta-analysis of 6 studies, 828 pts w/ conservatively tx prostate cancer (delayed hormones only, no rads or RP)
    - classified as either low-grade (Gleason 2-4), moderate-grade (Gleason 5-7) or high-grade (Gleason 8-10)
  - disease specific survival poor for high-grade at 10 yrs: low or moderate grade (87%), high-grade (34%)
  - risk of mets increases w/ grade at 10 years: low grade (19%), moderate grade (42%), high-grade (74%)
    - potential unknown selection biases: only 60% of cases included in final analysis, and most studies not randomized or population based
- Albertsen (1995 JAMA): long term survival in men w/ localized prostate cancer treated conservatively
  - 450 men aged 65-75 w/ clinically localized prostate cancer treated w/ delayed or immediate hormones only
    - classified as either low-grade (Gleason 2-4), moderate-grade (Gleason 5-7) or high-grade (Gleason 8-10)
  - overall, 34% died of prostate cancer
  - cancer-specific mortality at 10 yrs / 15 yrs:
    - low-grade: 9% / 9% → minimal risk of dying of prostate cancer
    - moderate-grade: 24% / 28%
    - high-grade: 46% / 51%
  - Gleason score: most powerful predictor of survival

#### **What is the chance of being biochemically disease-free 5 years after RP?**

- 77-80%, seen on several studies

#### **What are the clinical and biochemical outcomes for T1-2 disease after RP?**

- PSA should decline to undetectable levels
  - rising PSA almost always precedes clinical recurrence, usually by 6-8 years (Pound, 1999)
  - 15% of men after RP develop PSA progression (Pound)
- recurrence of prostate cancer = PSA > 0.4 and rising (or PSA > 0.2)
  - 5-15% of recurrences happen later than 5 yrs post-RP → **most recurrences occur within 5 yrs of RP**
  - failure after RP usually due to understaging
- **5 year PSA-nonprogression rates 77-80%**
- Hull (2001 JUrol): cancer control w/ RP alone
  - 1000 men w/ cT1-2 disease treated w/ RP and PLND alone before recurrence
    - 10 yr progression free survival 75%
    - 10 yr mets free survival 84%
    - 10 yr cancer specific survival 97%
  - for pT3 disease, 71% of ECE and 34% of SV involved pts w/ LN -ve free of progression at 10 yrs

#### **What are the prognostic factors that predict disease recurrence after RP?**

- Clinical
  - clinical stage: as stage increases, so does chance for recurrence
  - biopsy Gleason grade: as tumour becomes less differentiated, increased chance for recurrence
  - preoperative serum PSA
- Pathologic
  - **pathologic stage: single most powerful prognostic factor**
  - +ve margins

## **Chapter 89 Questions - RP.docrostatectomy**

- specimen Gleason grade: larger the proportion of high-grade disease, the worse the prognosis
- Postop
  - time to biochemical recurrence (2 y cutoff)
  - PSADT (10mo)

### **What steps may be performed to reduce the rate of +ve margins in RP?**

- wide dissection around apex
- deep dissection beneath Denonvilliers'
- selective resection of NVB
- division of BN proximally, away from prostate

### **What are the clinical and biochemical outcomes after RP for T3 disease?**

- prognosis is poor as most pts already have occult mets
  - if palpable beyond prostate into lateral sulci or SV, LN mets present in 30-50% of pts
- overall clinical nonprogression: 67% at 10 years, 61% at 15yrs
- RP is well tolerated in pts w/ T3 disease w/ minimal morbidity
  - no increased risk of UI or perioperative complications vs. T1-2 disease
- no change w/ neoadjuvant hormones
- external beam radiation + 3 years of LHRH agonist provides a survival advantage in pts w/ locally advanced disease vs. radiation alone (Bolla, 1997)

### **What are the criteria required to perform RP in pts w/ T3 disease?**

- low comorbidity and 10 yr life expectancy
- histologic documentation of prostate ca
- no significant extension to pelvic sidewalls or involvement of bladder base or trigone (-ve cysto)
- no evidence of mets

### **What factors may contribute to the development of BN contracture after RP?**

- prior TURP
- excessive intraoperative blood loss
- urine leak
  - overall incidence of anastomotic stricture: 0.5%-9%

### **What is the incidence of UI after RP?**

- < 10% in centers of excellence

### **What are the factors associated w/ an increased chance of regaining continence after RP?**

- younger age
- preservation of both NVB
- **preservation of functional urethral length**
- modification of anastomotic technique: avoid retraction of urethra, small bite of urethra, fully everted bladder neck
- absence of anastomotic stricture

### **How long does it take to regain continence post-RP?**

- median time to recovery 1.5months
- improvement for up to 1-2 years

### **How does one investigate and treat post-RP UI?**

- **defer invasive treatment for UI for 1year post-RP**
- cysto to r/o anastomotic stricture
- UDS
  - bladder dysfunction: anticholinergic +/- imipramine, fluid restriction, timed voiding, bladder augment
  - sphincteric injury: collagen (usually doesn't work) or AUS

### **What are the factors associated w/ regaining potency after RP?**

- patient age <50
- erectile function pre-op
- preservation of one or both NVB

What are the chances of potency post-RP?



## Chapter 89 Questions - RP.docrostatectomy

- men < 50: 90% potent if 1-2 NVB saved
- bilateral NVB saved: 30-68% potent overall
- one NVB saved: 10-47% potent overall

### What treatments can be instituted to improve chance of potency post-RP?

- early post-op medical therapy
  - injection therapy w/ alprostadil: improves cavernous oxygenation, limiting hypoxia-induced tissue damage
  - Viagra: may prevent post-op scarring of cavernous tissue
- sural nerve grafting: small studies

### What are the indications for RP?

- must be likely to be cured
- must live long enough to benefit from cure

### What factors may contraindicate RP?

- age: no cutoff, but life expectancy > 70-75 yrs may preclude benefit of cure
- stage: surgical tx only appropriate for T1-2, or small T3a in absence of mets
- PSA: no cutoff, but few pts w/ PSA > 100 have localized cancer
- Gleason: none – early detection may cure high grade disease
  - WW may be more appropriate for men w/ well-differentiated cancers

### How are pts usually stratified into treatment arms for prostate ca?

- staging and individual prognostic evaluation
- determine if treatment is to be instituted
  - low-risk tumours: deferred tx, watchful waiting, brachytherapy
  - intermediate risk tumours: RP or external rads
  - high-risk tumours: combined modality tx
- Partin tables predict probability of tumour being at specific pathologic stage
- Kattan tables predict probability of treatment failure after RP

### How do watchful waiting and RP compare in terms of survival?

- Holmberg (NEJM 2002): RP vs. WW in T1-2 disease
  - 695 men < 75 yrs w/ T1-2 disease randomized (327 WW + 297 RP)
    - 75-80% T2 disease, 70% Gleason 5-7, but 40% presented w/ sx
    - PSA > 10 in almost 50%, > 20 in 20%
  - RP reduced prostate cancer mortality by 50%, but NNT 17:1
    - lower risk of distant mets in RP group
  - **reduced DSS, but no change in overall survival**
  - many pts followed pre-PSA era
- PIVOT (Prostate Cancer Intervention versus Observation trial) study: RP vs. WW in PSA era

### How does neoadjuvant hormonal therapy affect pts post-RP?

- reduces rate of +ve surgical margins from 47-22%
- reduces pre-operative PSA by 96%
- reduces prostatic volume by 34%
- no difference in progression
- Gleave/Klotz (JUrol 2001): 3mo vs. 8mo neoadjuvant hormones before RP
  - 547 men w/ T1-2 prostate cancer randomized to get 3 or 8 months of leuprolide 7.5mg IM qmo+ flutamide 250mg PO TID
  - PSA dropped to < 0.1 in 43% vs. 75% (3 vs. 8mo)
  - TRUS determined prostate volume decreased from 40→25cc b/w 3 and 8 mo
  - +ve margin rates decreased in 8mo group (12% vs. 23%)

### What are the disadvantages of neoadjuvant hormones?

- causes periprostic fibrosis, obscuring natural tissue planes
  - increased chance +ve margins
  - may mask +ve margins
  - may reduce probability of erections postop
- shrinks tumour mass, difficult to palpate intraoperatively
- additional expense

## Chapter 89 Questions - RP.docrostatectomy

- may delay definitive tx

### What is the incidence of +ve LN in pts w/ clinically localized prostate cancer?

- 2-7%: much lower than previous rates of 20% pre-PSA

### What is the role of adjuvant rads/hormones in LN +ve prostate cancer?

- radiotherapy does not have a role in these pts
- immediate antiandrogen tx after RP improves survival and reduces risk of recurrence in pts w/ + LN (Messing 1999)

### Which pts should receive postop rads?

- +ve margins and undetectable PSA → 40-50% of these pts develop biochemical recurrence without rads
  - absence of SV invasion (usually have distant mets later anyway)
  - absence of LN mets

### What is the actuarial time from PSA elevation to time of radiographic mets?

- 8 yrs: Pound, 1999

### What factors can predict probability and time to progression of metastatic prostate ca?

- time to biochemical progression (< or > 2 years)
- Gleason score of RP specimen (5-7 vs. 8-10)
- PSA doubling time post-op (> or < 10 months)

### What factors can predict local vs. distant recurrence of disease?

- Local recurrence → give pelvic radiation
  - histologically N LN and SV
  - Gleason 7 or less
  - time to biochemical recurrence > 1 yr
  - PSA doubling time > 10months
- Distant recurrence → give hormonal therapy
  - LN or SV involvement
  - Gleason score > 7
  - biochemical failure < 6mo post-RP
  - PSA doubling time < 6mo

### What findings are associated w/ improved response to salvage rads?

- low stage
- low grade
- rads initiated w/ PSA < 2
- rads > 64 Gy

### What are the requirements for a pt to receive salvage RP?

- excellent health w/ life expectancy of > 10 yrs
- no evidence of mets
- clinically localized prostate cancer prior to rads
- clinically localized at recurrence
- highly motivated pt who accepts higher morbidity

### What is the chance of UI after salvage RP?

- **58% have persistent leakage → ++UI after salvage radiation**
- 20% require AUS
- 27% develop anastomotic strictures
- ED in ~100%

### What are the results after salvage RP?

- cancer often advanced by the time pts and doctors accept operation
  - Rogers, 1995: nonprogression rates at 5 and 10 years: 57% and 35%
    - overall survival: 90% at 5yrs, 70% at 10 years

### Preoperative PSA Velocity and the risk of death from prostate cancer after RP: NEJM 2004 (D'Amico)

- 1804 men in prospective screening for prostate cancer from 1989-2002

### **Chapter 89 Questions - RP.docrostatectomy**

- 1095 pts w/ localized prostate cancer
- all pts had DRE, PSA, and TRUS/bx
- PSA velocity  $> 2.00$  more likely associated w/ death from prostate cancer or from any cause
  - increasing PSA at dx, T2 disease, and Gleason 8-10 also predicted death from prostate cancer





## **Chapter 90**

### **• Anatomic Radical Retropubic Prostatectomy •**

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#### **What is the vascular supply to the prostate?**

- arterial
  - inferior vesical: divides into 2 groups
    - urethral group: enter prostate at posterolateral vesicoprostatic junction, supply BN
    - capsular group: run along pelvic sidewall, supply outer prostate
- venous
  - drain into Santorini's plexus
    - deep dorsal vein of penis leaves penis under Buck's fascia, dividing into 3 branches

#### **What is the neural supply to the prostate?**

- parasympathetic
  - preganglionic fibers arise from S2-4
- sympathetic
  - thoracolumbar center at L1-2

#### **Where do the NVB lie with respect to the urethra?**

- at membranous urethra, lie at 3 and 9 o'clock

#### **What fascia surround the prostate?**

- Denonvilliers'
  - located b/w anterior wall of rectum and prostate
  - 2 layers: cannot distinguish b/w them, must excise both
- prostatic fascia
  - NVB and blood supply runs b/w prostatic fascia and levator fascia
- levator fascia

#### **What is the anatomy of the external sphincter?**

- signet-ring shaped, broad at its base, narrowing as it passes through the urogenital hiatus to meet apex of prostate
- fibers do not meet posteriorly → omega shaped
  - edges fuse posteriorly w/ perineal body
- only fine, type I (slow-twitch) fibers: for tonic contraction

#### **What is the preop preparation needed for RP?**

- defer OR for 6-8 weeks post bx, 12 weeks post-TURP
- donate autologous if necessary
- avoid vitamin E, ASA, NSAIDs
- CF day prior to OR
- 1 bottle Mg Citrate in evening preop
- enema day of OR
- 1 dose 2<sup>nd</sup> generation cephalosporin pre incision

#### **Describe the surgical technique for RRP.**

- Anaesthesia
  - spinal or epidural: less blood loss, less PE
- Incision
  - pt supine
  - break table: may cause more pain, ileus
  - 16F foley
  - midline extraperitoneal lower abdo incision from pubis to umbilicus
  - separate rectus muscles, sharply open transversalis fascia to expose space of Retzius

## Chapter 90 Questions - RRP.doc

- Lymphadenectomy (only if Gleason > 7, abnormal feeling LN)
  - mobilize peritoneum laterally to expose iliacs
    - preserve soft tissue covering external iliac containing lymphatics
  - place Balfour/self-retaining retractor
  - divide adventitia over external iliac
  - dissect beneath external iliac vein to pelvic sidewall, inferiorly to femoral canal, superiorly to bifurcation of common iliac
  - ID and preserve obturator nerve, remove obturator nodes
- Exposure
  - 2.5 power loupes
  - retract bladder superiorly w/ wide malleable
- Incise endopelvic fascia (EPF)
  - enter EPF where it reflects over the pelvic sidewall where fascia is transparent
  - visualize bulging lateral venous plexus
  - extend incision in EPF anteromedially toward puboprostatics
  - palpate lateral surface of prostate
- Divide puboprostatic ligaments
  - remove fibrofatty tissue covering superficial branch of dorsal vein
  - sponge stick to push prostate posteriorly, scissors used to divide ligaments
  - expose junction b/w apex of prostate and anterior surface of dorsal venous complex
  - preserve pubourethral ligaments
- Divide dorsal venous complex (DVC)
  - 3-0 Monocryl passed superficially through DVC just distal to prostatic apex
  - reverse needle in driver, place same stitch through perichondrium of pubis and tie
  - Metz to divide DVC: start on L
  - oversee superficial edges of striated urethral sphincter-DVC w/ 3-0 Monocryl
- Divide urethra
  - pass R-angle clamp (or L-handed McDougall) under urethra at apex
  - divide anterior 2/3 of urethra w/ scissors
    - can place distal sutures at 12, 2, 5, 7, 10 o'clock
  - divide, clamp, and remove catheter
  - divide posterior band of urethra
  - divide posterior portion of striated urethral sphincter complex
- ID and preserve NVB
  - divide superficial prostatic fascia
  - ID NVB at apex, dissect posteriorly by spreading a R angle gently from apex to base
  - Excise lateral pelvic fascia and NVB if:
    - induration in lateral pelvic fascia
    - adherence of NVB to prostate during release
    - inadequate tissue covering posterolateral surface of prostate
- Posterior dissection and division of lateral pedicles
  - attachment in midline b/w rectum and Denonvilliers' fascia is divided in midline posteriorly
  - look for prominent arterial branch from NVB over SV to supply prostatic base
    - NVB no longer tethered to prostate, fall laterally
  - divide lateral pedicles, use clips
- Division of BN
  - divide BN anteriorly at prostatovesicular junction
  - observe for UOs
  - divide posterior BN
  - retract BN w/ Allis, divide vas deferens w/ hemoclips
- Excision of SV
  - dissect SV from surrounding structures
  - stay close to SV when ligating small vessels w/ small clips
- BN closure
  - tennis racket closure of BN w/ 2-0 chromic
  - 4-0 chromic to evert bladder mucosa

## What are the complications of RRP?

- Intraoperative
  - hemorrhage

## Chapter 90 Questions - RRP.doc

- tx: packing, suture
- division of DVC and oversew
- obturator nerve injury
- rectal injury
- ureteral injury
- Postoperative
  - delayed bleed → if require transfusion to support BP post-op, should bring back to OR to evacuate hematoma
    - will decrease risk of postop BN contracture
  - incontinence: usually due to ISD
    - complete control in 92%, SUI in 8% (2% change pad > 1 per day, 0.3% required AUS)
  - ED

### How does one tx a rectal injury during RRP?

- freshen ends of wound
- 2 layer closure
- Copious irrigation
- interpose omentum
- dilate anal sphincter
- broad-spec abx
- diverting colostomy if pt received rads or large injury/spillage







## Chapter 91

### • Radical Perineal Prostatectomy •

---

#### **What are the advantages and disadvantages of RPP?**

- Advantages
  - clear exposure and access to prostatic apex
  - less blood loss: don't transect dorsal venous complex
  - tie vesicourethral anastomosis under direct vision
  - useful if previous abdominal or pelvic surgery
- Disadvantages
  - cannot approach LN
  - exaggerated lithotomy required
  - difficult if prostate > 100cc

#### **How can one determine in the office if a pt can tolerate exaggerated lithotomy?**

- ask pt to lie supine, bring knees to their chest
- inability to do this is a contraindication

#### **What are the requirements for nerve-sparing RP?**

- good potency w/ strong desire to preserve it
- acceptance of the pt of risk of iatrogenic +ve margin
- little or no clinically recognized adjacent tumour
- NVB cleanly dissected off prostate

#### **Describe the procedure of radical perineal prostatectomy.**

- Anaesthesia
  - epidural vs. GA
- Positioning
  - buttocks beyond end of table
  - shoulder restraints w/ padding
  - ankles and feet in egg-crate, placed in stirrups
  - exaggerated lithotomy
  - beanbag under sacrum
  - avoid Trendelenberg
  - shave perineum
- Incision
  - approach through or around external rectal sphincter
  - curved Lowsley retractor placed in bladder, opened, left in place
  - incision: make from 1 ischial tuberosity to other, w/ apex approximately 1.5cm above the anus, anterior to mucocutaneous pigmented line
  - ischiorectal fossa on either side of rectum bluntly developed
  - palpate rectum, tunnel beneath superficial central tendon → divide w/ cautery
  - sweep muscle fibers of external rectal sphincter upward and lateral → **do not incise**
  - follow rectal wall to perineal body
- Dissection
  - transect rectourethralis to apex of prostate
  - identify Denonvilliers'
  - rectal surface separated from posterior layer of Denonvilliers'
  - incise rectum from base of prostate sharply
    - rectal wall usually adherent to prostate-SV junction
  - identify NVB bilaterally: transected or saved

## Chapter 91 Questions - RPP.docrostatectomy

- develop spaces lateral to prostate
- place Thompson self-retaining retractor
- posterior membranous urethra opened distal to apex of prostate
- replace curved Lowsley retractor w/ straight Lowsley retractor
- transect anterior urethra
- follow anterior prostate to anterior BN
- transect puboprostatics
- incise anterior BN
- incise lateral attachments to BN
- transect trigone 1cm distal to UOs
- dissect ampullae of vasa, transect
- dissect out SVs
- ligate pedicles bilaterally
- remove specimen
- Anastomosis
  - pass 18F red rubber through urethra
  - anast w/ 2-0 SAS: 3 stitches anteriorly at 11, 12, 1 o'clock
  - close BN in tennis racket fashion
  - complete anastomosis posteriorly
  - observe for UOs: can use indigo carmine
  - pass Foley into bladder
  - irrigate wound
  - place drains
- Closure
  - reapproximate levators w/ 2-0 SAS
  - reapproximate central tendon w/ 2-0 SAS
  - obliterate dead space
  - close incision w/ 4-0 subcuticular
- Postoperative management
  - pain control
  - inflatable donut
  - nothing PR
  - Colace
  - remove drains POD2

### What are the complications of RPP?

- rectal injury
- fecal fistula
- fecal incontinence
- inadvertent Foley removal
- UI
- retention
- ED

### When is the most likely time for rectal injury to occur during RPP?

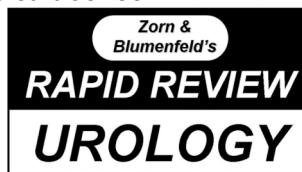
- during division of rectourethralis or:
- establishing plane b/w rectum and prostate and SVs

### What is the treatment of fistula after RPP?

- diverting colostomy x 3-4 months
- if requires OR to repair, place gracilis muscle as interposition tissue
- VCUG via SP tube in 2-3 weeks postop

### What is the incidence of fecal incontinence post-RPP?

- 16% (8% in RRP)
- **anal dilation itself can cause fecal incontinence in up to 20%**



## Chapter 92

### • Radiation Treatment for Prostate Cancer •

---

#### **What 2 major advances in radiotherapy for prostate cancer have occurred since the 1980s?**

- generation of linear accelerators and conformal techniques capable of delivering high doses of radiation deep into pelvis and limiting dose to rectum, urethra, femoral heads, and BN
- image-guided techniques for insertion of radioactive sources directly into prostate

#### **Why does brachytherapy have a very rapid dose falloff (few millimeters)?**

- due to low energy of radioactive sources used
  - 21 keV: palladium 103
  - 28 keV: iodine 125
- requires mm precision in placement

#### **What are the prognostic factors that predict recurrence after external-beam RT?**

- Pre-treatment
  - PSA level
  - biopsy Gleason grade
  - clinical stage
  - % cores +ve for cancer → predicts time to biochemical failure
- Post-treatment
  - **PSA nadir: strongest independent RF for failure**
  - time to nadir
  - post-radiation biopsy

#### **How can one classify pts into a risk category based on pre-treatment prognostic factors?**

- Low risk: >85% 5-year PSA failure-free survival
  - T1c-T2a
  - PSA < 10
  - biopsy Gleason 6 or less
  - % cores +ve < 33%
- Intermediate risk: 50% 5-year PSA failure-free survival
  - T2b
  - PSA 10-20
  - biopsy Gleason 7
  - % cores +ve 33-50%
- High risk: 33% 5-year PSA failure-free survival
  - T2c
  - PSA > 20
  - biopsy Gleason 8 or more
  - % cores +ve > 50%

#### **Why does RT cause a decrease in serum PSA?**

- atrophy and reduction in size and # of nonmalignant acini

#### **What PSA nadir post-RT are associated w/ cure vs. failure?**

- desirable PSA nadir is < 0.5: 10-20% biochemical failure at 5 yrs
- PSA nadir > 1: 63-100% biochemical failure at 5 yrs

#### **What is the ASTRO definition of biochemical failure post-RT?**

- 3 successive increases in PSA
- PSAs must be 3-4mo apart in 1<sup>st</sup> 2 yrs, every 6mo apart after 2y

## **Chapter 92 Questions - Rads for prostate ca.docnccer**

### **How does PSA nadir, and time to PSA nadir affect survival?**

- inversely proportional
  - those that reach nadir earlier (10-12mo) tend to fail distantly: nadir 2-3ng/mL
  - median time to nadir in pts that remain free from failure is 22-33 months: nadir 0.4-0.5ng/mL
  - local failures tend to nadir intermediately 17-20 mo: 5-10ng/mL

### **Why does PSA nadir occur so long after RT?**

- RT does not cause immediate cell death
- dsDNA chromosomal breaks are not immediately fatal, but do not permit successful cell reproduction
- PSA declines progressively until rate of growth of surviving prostate cancer cells > death rate of those fatally damaged

### **What are the sources of PSA after RT?**

- residual benign prostatic epithelium
- residual local prostate cancer
- subclinical disseminated micromets

### **What is the role of neoadjuvant hormone treatment before RT?**

- neoadjuvant hormones often used before rads, esp if pts have more locally advanced or high-risk disease

### **When is the optimal time to biopsy after RT to determine effectiveness of treatment?**

- 30-36 months
- biopsies taken before histologic resolution is complete show marked radiation effect
  - fatally damaged cells can survive a limited # of divisions before dying off
  - 30% of +ve biopsies at 12-18months resolved by 30months

### **What major issues prevent accurate interpretation of post-RT biopsy?**

- uncertain optimum timing
- interpretation of indeterminate biopsies
- sampling error

### **How can one grade GU and GI morbidity post-RT?**

- RTOG GI and GU morbidity scales
  - GI
    - Grade 1: sx not requiring medical intervention
    - Grade 2: > 2 antidiarrheals/wk, regular nonnarcotic use, occ.transfusion, occ. steroids, occ. dilation, intermittent pads
    - Grade 3: > 2 antidiarrheals/day, regular narcotic use, frequent transfusion, steroid enemas, hyperbaric oxygen for ulcers, daily pad use
    - Grade 4: perforation, life-threatening bleeding, surgical repair
    - Grade 5: fatal toxicity
  - GU
    - Grade 1: sx not requiring medical intervention
    - Grade 2: moderate frequency, generalized telangectasias, intermittent gross hematuria
    - Grade 3: severe frequency/dysuria, severe generalized telangectasias, frequent hematuria, reduced capacity < 150cc
    - Grade 4: necrosis, contracted bladder (<100cc), severe hemorrhagic cystitis
    - Grade 5: fatal toxicity

### **What is the incidence of ED after RT?**

- gradually worsens over time
  - 40% by 5 years (MSK 1999)
- 3 months
  - no erections 5%
  - inadequate erections 55%
  - difficult erections 50%
- 12 months
  - no erections 20%
  - inadequate erections 60%
  - difficult erections 25%

## **Chapter 92 Questions - Rads for prostate ca.docnccr**

### **How good is cancer control after conformal RT for prostate cancer?**

- long term data not available
- University of Michigan 1997, 707 pts w/ 3D conformal rads up to 80Gy (most > 69Gy)
  - favourable features: T1-2, Gleason <7, PSA<10
    - 75% 5 year biochemical relapse free
  - unfavourable features: T3-4, Gleason >7, PSA>10
    - 37% 5 year biochemical relapse free
- dose escalation improves cancer-free survival (Hanks, 2000) → 1600 pts w/ conformal rads, 5 year disease free state w/ less than or greater than 76Gy
  - favourable features: PSA < 10 (all do well), PSA 10-20 (85% vs. 70%), PSA > 20 (65% vs. 20%)
  - unfavourable features: PSA < 10 (90% vs. 70%), PSA 10-20 (80% vs. 50%), PSA > 20 (none OK, no benefit to dose escalation)

### **What is IMRT?**

- intensity modulated RT: maximizes dose to prostate, minimizes dose to adjacent tissues

### **What are the advantages in using heavy particle beams over conventional rads for prostate cancer?**

- more densely destructive in tissue
- damage they create is less easily repaired by tumour cells
- travel differently in tissue: Bragg peak → sharp cutoff in dose at end of particles range in tissue
  - results seem to be similar to conformal rads

### **What are the most commonly used particles from heavy particle beams?**

- protons and neutrons

### **What are the choices of isotopes for permanent seed implantation?**

- iodine 125
  - low energy xrays at 27 keV w/ t<sup>1/2</sup> of 60d
- palladium 103
  - 21 keV, t<sup>1/2</sup> of 17d → higher-activity seeds required
- no RCT comparing the two types

### **What happens to PSA post brachy?**

- 1<sup>st</sup> 3 months: increases in 25%
- rapid decline over 12-18months
- continues to decline for 5 yrs
- biochemical recurrence
  - 35-95% free from relapse ~ 5 yrs post brachy

### **What is the definition of treatment failure post-brachy?**

- controversial: absolute level of 0.5-1.0ng/mL suggested

### **What are the results of post-brachy prostate biopsy?**

- +ve biopsy rate of 3-26%

### **Describe the procedure of real-time MRI guided brachytherapy.**

- pt in lithotomy, anaesthetized
- Foley inserted and clamped
- MRI template secured to MR table and placed against pts perineum
- rectal obturator placed into rectum and secured to template
- MR slices obtained
- catheters using preloaded sources inserted, position in coronal, sagittal, and axial planes identified in real time

### **What are the complications of brachytherapy?**

- urinary retention: 1-5%
  - 96% void spontaneously after Foley removed
  - 5% require alpha blockers for > 1 month
- LUTS
  - higher rate of GU toxicity compared to external beam RT
  - IPSS increases significantly after brachy, remains high x 3months
  - worse LUTS w/ larger prostates (> 60cc)

## Chapter 92 Questions - Rads for prostate ca.docncer

- rectal toxicity
  - rectal bleeding due to radiation proctitis
  - minor bleeding in 1-4%
  - colostomy rate of 0.3%
- ED
  - potency rates better compared w/ external beam
  - potency maintained in 79% of brachy pts (vs. 68% external beam rads): Zelefsky 1999
  - Viagra works in 80% of pts w/ ED post-brachy

### How can brachytherapy be combined w/ external beam RT?

- brachy used as a boost before or after external beam RT
- pts generally have higher stage disease
- 45 Gy delivered externally
- implantation boost is 60-70% of dose level for implantation alone
- more dose received by rectum, less by urethra

### What are the results after external beam rads w/ brachy boost?

- 5 yr biochemical-recurrence free survival from 90-95%
- 10 yr: 70-75%

### What is HDR brachytherapy?

- high dose rate brachytherapy
  - high-activity iridium 192 sources, emits gamma radiation at 400 keV (kiloelectron-Volt)
  - administered for a predetermined time under computer guidance
  - delivered as a boost before or after external beam radiation
  - slightly higher % of prostate receives full prescribed dose of radiation

### What is the role of androgen suppression in combination with radiation?

- short-duration hormone therapy can reduce local tumour burden requiring rads
- longer adjuvant hormones can be used to suppress systemic disease outside the radiation field
- Bolla 1997: rads + 3 yrs Zoladex vs. rads alone improves survival in LN-ve pts
- Pilepich 1995: 4 months of neoadjuvant hormones leads to improved local control, reduction in distant mets, and prolonged biochemical and disease-free survival in men w/ bulky locally advanced disease
- Akakura (1999 Urology): RP + hormones vs. rads + hormones in T2-4 prostate cancer
  - 100 pts w/ B2-C prostate cancer randomized to either RP or rads, followed by hormones (DES 300mg) in both groups
    - 50Gy to pelvis, 20Gy boost to prostate: 4 field box
  - overall survival and disease specific survival higher in surgery group

### What is the optimal duration of neoadjuvant hormones before RT?

- undetermined
  - RTOG 99-10 to compare 28 weeks vs. 8 weeks followed by rads + MAB in intermediate risk prostate cancer

### What studies exist that show the advantage of androgen deprivation combined w/ RT?

- Pilepich 1995: neoadjuvant hormones (RTOG 86-10)
  - pts w/ large T2b-T4 tumours randomized to 4months MAB w/ RT given after 2mo
  - improved local control, disease-free survival, and freedom from mets
- Bolla 1997 (EORTC study)
  - 415 pts randomized (208 to rads, 207 to rads + 3 yrs of LHRH agonist)
    - 50Gy to pelvis, 20Gy boost to prostate: 4 field box
    - 3.6mg goserelin qmo + 1mo of cyproterone initially to prevent flare
  - adjuvant rads vs. rads + LHRH agonist
    - significant difference in clinical DSS, cancer-specific survival, and OS
    - 5yr DSS (78% vs. 94%) and OS (62% vs. 79%) for rads alone vs. rads+LHRH

### What studies show the benefit of combined RT and hormones in LN +ve disease?

- Messing 1999
  - survival advantage in randomized study of immediate vs. delayed androgen suppression in pts w/ LN +ve disease

### What are the indications for RT use for palliation?

## Chapter 92 Questions - Rads for prostate ca.docncer

- bony mets
- spinal cord compression

### What are the sx of bony mets?

- localized pain:
  - continuous and unrelenting
  - etiology not known → ?irritation of periosteal membrane or release of biologic mediators

### How can one dx bony mets?

- P/E, plain xray, bone scan
- CT/MR if other tests -ve

### What is the response rate of bony mets to rads?

- 85-100% overall response
  - 8 Gy x 1
  - 3 Gy x 10 often used

### What are the indications for prophylactic surgical fixation of bony mets?

- intramedullary lytic lesion equal or > 50% of cross-sectional diameter of bone
- lytic lesion involving length of cortex equal to or > cross-sectional diameter of bone or > 2.5cm in axial length

### What are the sx of spinal cord compression?

- pain: in 95% of pts
  - precedes dx of spinal cord compression by 4 months
- paraplegia
  - rapidly progresses w/i hours
  - **return of function infrequent after paraplegia develops**
- autonomic dysfunction

### What are the indications for pre-radiation surgical fixation of vertebral # w/ cord compression?

- treat all pts w/ suspected cord compression w/ steroids
  - pathologic # w/ spinal instability
  - compression of spinal cord by bone
  - unknown tissue diagnosis
  - hx of previous rads to same area

### What is the tx of spinal cord compression?

- treat all pts w/ suspected cord compression w/ steroids
  - steroid therapy: dexamethasone 4-100mg loading dose, then 4-24mg q6h
- radiation

### What is the use of systemic radionuclide therapy?

- used in pts w/ hormone refractory disease

### What radionuclides are often used for systemic radionuclide therapy?

- <sup>32</sup>Phosphorus
- <sup>89</sup>Strontium
- <sup>186</sup>Rhenium
- <sup>153</sup>Samarium

### What is the toxicity of <sup>89</sup> strontium?

- hematologic: thrombocytopenia

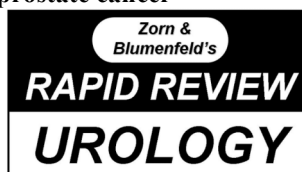
### Who gets salvage rads for recurrent prostate cancer after RP?

- PSA doubling time identifies pts that will respond
- Stephenson (JAMA 2004): salvage rads for recurrent prostate cancer after RP
  - 500 pts received rads for detectable/increasing PSA after RP
  - 50% experienced disease recurrence after rads, 10% had distant mets, 4% died from prostate cancer
    - 45% progression-free at 4 years
  - **predictors of progression: Gleason 8-10, PSA DT > 10mo, +ve margins, PSA < 2, SV involvement**

## **Chapter 92 Questions - Rads for prostate ca.docncer**

- PSA-DT < 10mo: 22% 4 yr progression free survival
- PSA-DT > 10mo: 77%
- if PSA > 2 after rads, is too late





## **Chapter 93**

### **• Cryotherapy for Prostate Cancer •**

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#### **What are the advantages of cryoablation of prostate cancer?**

- focal application w/ sparing of many normal tissues
- treatment of unresectable cancers
- minimal bleeding
- local anaesthetic effect
- predictable freezing pattern

#### **What does the frozen area look like on US?**

- well-marginated hyperechoic rim w/ acoustic shadowing

#### **Describe the mechanism of tissue destruction by cryotherapy.**

- ECF crystal formation leads to cellular destruction
  - increases osmotic pressure of unfrozen ECF, shifting water out of ICF → cellular dehydration
  - pH change due to abnormal electrolyte concentration, leading to denaturation of cellular proteins
  - thermal shock w/ damage to lipoproteins
- crystallization of water in ICF causes cellular membrane disruption
- cellular swelling due to fluid influx during thawing
- vascular stasis due to thrombosis after freezing

#### **What factors affect tissue destruction during cryoablation?**

- **velocity of cooling and thawing**
  - faster freezing and slower thawing will increase cellular destruction
- **lowest temp achieved:** need temp below  $-40^{\circ}\text{C}$  to completely destroy cells
  - unlikely to occur if temp above  $-20^{\circ}\text{C}$
- duration of freezing
  - prolonged freezing will increase tissue destruction
- number of freeze-thaw cycles
- presence of heat sinks
  - blood vessels in vicinity may prevent the achievement of target temperature

#### **How does a 2nd freeze-thaw cycle affect tissue destruction?**

- freezing of tissue results in a central zone of complete destruction, and peripheral zone of damaged tissue
- 2nd cycle significantly increases central zone of complete necrosis

#### **What types of cryogenic systems are available in the US?**

- CMS AccuProbe
  - liquid nitrogen cooled and compressed, 3 mm probe: 4cm ice ball
- Cryocare system
  - liquid argon, 8 3mm probes used, 4 cm ice ball
- Galil system
  - liquid argon, 17G needle probe, 2 cm ice ball

#### **What patient factors determine eligibility for cryotherapy?**

- cancer stage and grade
  - low volume, stage, and grade may be ideal for cryo
  - pts w/ more advanced disease at increased risk for biochemical recurrence, can use for local control
  - HRPc pts can be treated w/ cryo to prevent retention or bleeding
- prostate size
  - large prostates difficult to treat
  - if volume  $> 50\text{cc}$ , neoadjuvant hormones to shrink prostate may be useful

### Chapter 93 Questions - Cryotherapy for prostate cancer

- salvage therapy
  - previous rads increase chance of complications after cryo

#### Describe the technique of cryotherapy for prostate cancer.

- Preop preparation
  - staging: imaging, bone scan, CT
  - PSA
  - regional LN dissection: minilap or laparoscopic → if high risk for LN mets
  - neoadjuvant hormones if: gross ECE, SV invasion, prostate > 50cc
  - bowel prep: Mg citrate, enema
  - Foley catheter, bladder distended w/ NS
- TRUS and needle placement
  - 6 18G needles placed in prostate under TRUS guidance
  - needles placed **greater than 8mm** from urethra to prevent urethral freezing
  - guidewire placed through needles, dilate to 12F, 12F cannulas placed
- Thermosensor and urethral warmer placement
  - temperatures monitored at apex, external sphincter, along Denonvilliers', edge of tumour
  - 18G needles placed under TRUS, thermosensors passed through needles
  - urethral warmer placed, started
- cryoprobe placement and monitoring of freezing process
  - cannulas retracted to expose tip of each probe
  - once ice formed, everything anterior to ice is hidden by shadow: **start anterior probes first**
  - iceball extends anteriorly and laterally
    - beyond apex, 2-4mm laterally into periprostatic tissue, and into muscularis propria of rectum
  - posterior iceballs extend to muscularis propria of rectal wall
  - 2 freeze-thaw cycles
  - place additional needles into prostate/SV if necessary
- Postop care
  - d/c home same day
  - **Foley/SP x 3 weeks**

#### What happens to PSA after cryotherapy?

- PSA rises to very high level immediately after cryo
- PSA nadir usually at 3 months

#### What is the TRUS appearance of the prostate after cryo?

- immediately: no difference
- 3 months: necrosis, heterogeneous echo pattern
- 6 months: small gland w/ obscured boundary consistent w/ periprostatic fibrosis

#### What is the +ve biopsy rate after cryo?

- depends on clinical stage pre-treatment
  - T1-2 disease: 9%
  - T3 disease: 22-25%
- depends on # of freeze-thaw cycles
  - one cycle: 30-64%
  - 2 cycles: 9-11%
- depends on presence of thermosensors to ensure appropriate temperature
  - no thermosensors: 83%
  - thermosensors: 10%

#### What areas of the prostate are more likely to be sites of treatment failure?

- apex: 10% failure
- SV: 44% failure
  - base and midgland have fewest recurrences

#### What is the acceptable level of PSA nadir to be achieved after cryo?

- not known, like radiation
  - biochemical failure lowest if nadir < 0.1ng/mL (21%)
  - biopsy failure lowest if nadir < 0.1 (1.5%) or < 0.4 (10%)

## Chapter 93 Questions - Cryo.doctherapy for prostate cancer

- high rate of +ve biopsy if nadir > 0.5ng/mL (55%)

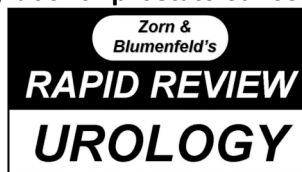
### What are the results of salvage cryotherapy for pts w/ local failure after rads?

- biochemical free survival 66% and -ve biopsy in 93% if 2 freeze-thaw cycles
- significant complication rate: 73% UI, 67% obstruction

### What are the complications of cryotherapy?

- **ED: > 80%**
  - due to extension of iceball into NVB
  - also due to vessel injury
- incontinence: 2-10% if primary treatment, > 70% after radiation to some degree
- UTI
- tissue sloughing: 4-23%, usually 3-8 weeks after procedure, often if CIC
  - **necrotic prostate becomes infected → sloughs into urethra, ++ LUTS**
  - up to 44% post radiation
  - tx: antibiotics, Foley, TURP if needed to remove necrotic tissue
- pelvic and rectal pain: 0.4-11%, up to 26-77% if salvage cryo post-radiation
  - etiology unknown: may be rectal wall ischemia, extravasation of urine in periprostatic tissue, freezing of pelvic floor/pelvis
- penile numbness (10%): due to damage to dorsal nerve of penis
- rectourethral fistula: 0-3%, more common post-radiation (11%)
  - sx: watery diarrhea or pneumaturia
  - VCUG or CT to confirm
  - Foley drainage initially
  - formal fistula repair delayed until inflammation resolved: 4-6months
- urethral stricture
  - stricture at BN or prostatic urethra
  - VIU vs. dilation
- hydronephrosis (36% of salvage cryo): freezing of ureteral orifices
- small bowel obstruction (0.5%)
  - only occurs if iceball extends into peritoneum





## **Chapter 94**

### **• Hormonal Therapy of Prostate Cancer •**

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#### **What is the natural hx of metastatic prostate cancer?**

- 80-95% die in 5 years
- favourable response to endocrine tx is temporary → 100% become androgen independent at some point

#### **What are the sources of androgens in males?**

- Leydig cells in testes: 90-95%
  - testosterone converted to DHT in prostate by 5 $\alpha$ -reductase
  - T and DHT bound to SHBG
- adrenal androgens: 5-10%
  - produced in zona fasciculata and zona reticularis
  - DHEA and androstenedione
  - adrenal androgens bound to albumin in cclx

#### **What endocrine factors regulate T and DHT production?**

- under pituitary control by LH and ACTH

#### **Describe the hypothalamic pituitary axis that controls T regulation.**

- LHRH released from hypothalamus
  - stimulates pituitary to release LH and FSH
  - LH stimulates testes to release T and estrogens
  - T -ve feedback on hypothalamus
- CRF released from hypothalamus
  - stimulates pituitary to release ACTH
  - ACTH stimulates adrenal to release adrenal androgens and steroids
  - steroids -ve feedback on hypothalamus

#### **What mechanisms are available to achieve androgen deprivation?**

- surgical castration
- medical castration
  - estrogens: DES
  - LHRH agonists and antagonists
    - synthetic LHRH agonists may times more powerful than natural
    - after initial period of stimulation, LHRH agonist causes suppression of LH and castrate levels of T
    - buserelin 3.6mg q1mo
    - goserelin 3.6mg
    - luprolide 3.75mg
    - triptorelin 3.75mg
  - antiandrogens
    - steroidal
    - nonsteroidal: pure antiandrogens
  - MAB
  - 5 $\alpha$ -reductase inhibition
- timing
  - immediate vs. delayed
  - adjuvant endocrine treatment
  - 2<sup>nd</sup> line endocrine treatment
  - intermittent endocrine treatment
  - step-up endocrine treatment: start w/ less aggressive/effective means of endocrine tx, castrate if needed → unproven
    - start w/ finasteride, step up to antiandrogen, then castration

#### **What are the prognostic factors for survival in pts w/ advanced prostate cancer?**

## Chapter 94 Questions - Hormone therapy.doc for prostate cancer

- mets
- Gleason grade
- all TNM categories

### What is a "surrogate marker?"

- a factor that can replace survival as an end point

### What are the most important parameters in phase III studies of endocrine tx of prostate cancer?

- overall survival
- disease specific survival
- time to progression

### What is the role of PSA in predicting response to hormones?

- PSA at time of dx is not a good predictor of time to progression and survival in men w/ advanced disease
- PSA response to hormones correlates well w/ progression and survival
  - PSA < 10 at 6 months predicts good response

### What is the role of endocrine tx in prostate cancer?

- palliation
  - eliminates sx in most pts
  - **prolongs time to clinical progression**
  - possibly prolongs survival in some pts

### Does endocrine tx prolong survival in men w/ prostate cancer?

- not possible to have trial comparing endocrine tx vs. placebo
  - studies 1 and 2 of VACURG (Veterans Admin Cooperative Urological Research Group) compared hormones vs. placebo in stage 3 and stage 4 prostate cancer
    - survival independent of early or late initiation of treatment
    - early endocrine tx delays progression from stage 3 to stage 4

### What are the side effects of endocrine tx?

- andropause: decreased libido and potency, fatigue, fragility due to loss of muscle
  - decreased total/free/bioavailable T, increased SHBG
- decreased libido and sexual fn
- osteoporosis: BMD decreases over > 36mo, ? increased pathologic #
  - mortality rate significant w/ hip #
  - measure density w/ DEXA scan (dual energy Xray absorptiometry)
- anemia: decrease in Hgb from 10-25%
  - may be due to decrease in EPO from LHRH agonists
- hot flashes: occur in > 50% of men w/ castration
  - **due to periodic release of endogenous opioid peptides in the hypothalamus**
  - clonidine: no effect
  - cyproterone, megestrol, DES: good effect, some s/e
  - SSRI: significant reduction in hot flashes

### What is the treatment for osteopenia/osteoporosis associated w/ endocrine tx?

- stop smoking
- weight bearing exercises
  - has not been shown clearly to change osteoporosis, but decreases rate of falls (and #): helps w/ balance
- vit D, Ca: in all pts that are on hormonal therapy
- bisphosphonates
  - alendronate (Fosamax)
  - risedronate (Actonel)
  - pamidronate (Aredia): approved for metastatic breast cancer and MM, but not effective in metastatic prostate cancer
  - zoledronic acid (Zometa): 4 mg/5ml diluted in 100 mL NS IV over > 15 minutes q3-4 weeks x 9 mo
    - only one shown to be of benefit in prostate cancer pts to improve BMD in RCT
      - ◆ RCT of 643 pts, bone mets w/ 3 increasing PSA levels, PSA > 4 (JNCI Saad, 2002)
      - ◆ delays time to 1<sup>st</sup> SRE by 5-6mo, total SRE, and SMR related to placebo
    - most potent bisphosphonate
    - s/e: ARF, hypocalcemia, flu-like sx, anemia, N/V

## Chapter 94 Questions - Hormone therapy.doc for prostate cancer

- should be given to all men w/ progressive metastatic disease

### What are the advantages of surgical castration as endocrine tx of prostate cancer?

- under local anaesthesia as an outpt
- immediately effective
- no compliance problem
- cost low
- can place prosthetic for cosmesis

### Is castration as effective as other forms of management of prostate cancer?

- comparable to other medical methods
  - compared in many prospective randomized studies
  - VACURG Study 1: 5mg DES more effective than orch in preventing cancer death, no difference in OS
  - VACURG Study 2: 1mg DES smaller chance dying vs. 5mg DES → CVS mortality increased in 5mg group
  - EORTC study: orchiectomy vs. 1mg DES vs. MAB (castration + CPA)
    - no difference in progression and survival

### What is the time to plasma T nadir in surgical vs. medical castration?

- surgical: 8-9hrs
- DES: 1-2months
- LHRH agonists: 3-4 weeks

### What is the impact of castration in men w/ prostate cancer?

- same as other hormonal manipulation
  - loss of libido, ED
  - increased risk of osteoporosis
    - increased risk of #
    - mortality after hip #: M > F
    - overall 15 yr # rate 40% (in castrati) vs. 20% (in general pplx)
  - weight gain, obesity
  - anemia

### What is the effect of estrogens in the tx of prostate cancer?

- cause -ve feedback at level of hypothalamus
  - decrease LHRH and LH production
- estrogens do not have an additional effect on improving OS or DSS

### Why is DES not used now for prostate cancer?

- excessive mortality from CVS side effects
- reduced availability of medication
  - previously used doses from 0.2-1000mg per day (1mg TID usual dose)
  - polyestradiol phosphate IM 240mg q2-4weeks used in Scandinavia → no increase in CVS death

### What are the s/e of DES?

- increased cardiovascular death
- gynecomastia
- hot flashes

### How can one avoid the CVS s/e seen w/ PO DES?

- eliminate initial passage through portal system and liver
  - polyestradiol phosphate injection 240mg

### Why have LHRH antagonists clinically not been used yet?

- abarelix
  - high dose required
  - allergic reactions at injection sites

### What complications have occurred from the flare reaction seen w/ LHRH agonists?

- deterioration of bone pain
- radiologic evidence of acute progression

## Chapter 94 Questions - Hormone therapy.doc for prostate cancer

- paraplegia
- death

### How can one prevent clinical flare from LHRH agonist?

- use of pure or steroidal antiandrogen 1 week prior to initiation of LHRH agonist (or simultaneously)
  - 1 week of steroidal prior: causes prevention in peak of T and biochemical flare
  - simultaneous use: peak in T seen, but flare prevented

### What different antiandrogens are available?

- steroidal
  - cyproterone acetate
  - medroxyprogesterone acetate
- nonsteroidal (pure antiandrogens)
  - nilutamide (Anandron) 100mg PO TID: EtOH intolerance, poor adaptation for night vision, interstitial pneumonitis, gynecomastia
    - T  $\frac{1}{2}$  56 hrs
  - flutamide (Eulexin) 250mg PO TID: ++ diarrhea, hepatic dysfunction
    - T  $\frac{1}{2}$  4 hrs
  - bicalutamide (Casodex): 50-300mg PO OD: gynecomastia, breast tenderness

### Why do men get gynecomastia w/ the use of flutamide?

- rise of plasma estradiol simultaneously w/ rise of T under flutamide tx
  - due to increased aromatization of T

### Describe the mechanism of action for pure antiandrogens and steroidal antiandrogens.

- all bind to AR in competitive fashion
- pure antiandrogens (nonsteroidal)
  - block AR in diencephalon (area crucial for LHRH production)
  - block feedback mechanism that regulates T levels through LH
  - leads to LH increase
  - rise in plasma T temporary, self-limiting at 1.5X normal T levels
- steroidal antiandrogens
  - increase in LH and T inhibited by antigonadotropic effect
  - partial antigonadotropic effect are not associated w/ LH, T, or estradiol rise

### What are the advantages of CPA?

- PO use
  - dose: 100mg PO BID/TID
- immediately effective
- lack of CVS side effects

### What are the side effects of CPA?

- loss of libido: develop slowly over 8-12 mo
- ED (80%)
- CVS s/e
- hepatotoxicity
  - occasional abnormal LFTs
  - worse in flutamide than CPA
- hot flashes and gynecomastia: rare
  - **CPA 50-100mg PO OD can prevent hot flashes in men taking LHRH agonists**
- osteoporosis, muscle wasting, anemia: absent or less pronounced

### What are the results of pure antiandrogen as monotherapy?

- CPA
  - never been compared w/ castration or LHRH agonist
  - no difference b/w CPA and DES 3mg or estradiol IM or flutamide
- bicalutamide
  - 50mg vs. surgical castration: 3mo survival advantage for surgery
  - 150mg vs. surgical castration: slight advantage for surgery, equivalent in M0 disease
- flutamide



## Chapter 94 Questions - Hormone therapy.doc for prostate cancer

- vs. CPA: more gynecomastia, N/V, diarrhea, and LFT changes w/ flutamide
  - more CPA pts had no toxicity
- nilutamide
  - not recommended as monotherapy
  - s/e: EtOH intolerance, poor night vision, interstitial pneumonitis
- meta-analysis (Seidenfeld 2000): **trend to shorter OS in nonsteroidals** vs. castration or LHRH agonists, not stat. sig

### What are the advantages of pure antiandrogen as monotherapy?

- elevation of plasma T and estradiol prevents serious side effects of castration and long-term use of LHRH agonist
  - osteoporosis, spontaneous fracture, muscle wasting, anemia, fatigue

### What are the results of MAB for prostate cancer?

- DES 1mg vs. castration + CPA 200mg
  - no difference in progression rates, time to progression, and OS
- meta-analysis of 27 randomized trials (Prostate Cancer Trialists Collaborative Group 2000)
  - 5yr survival w/ MAB: 25.4% vs. 23.4% w/ castration or use of LHRH agonist → not significant
  - may only be useful in symptomatic pts w/ large tumour loads → pt population that will benefit the most from MAB remains unidentified
- Eisenberger 1998: no difference in survival

### What MAB regimens may be used?

- castration + LHRH agonist (or estrogen) + antiandrogen
  - nilutamide 300mg x 1day, then 150mg PO OD
  - flutamide 250mg PO TID
  - bicalutamide 50mg PO OD

### What is the antiandrogen withdrawal syndrome?

- 40% of pts who progress on MAB w/ use of flutamide show a remission after d/c tx
  - thought to be due to mutation in AR
  - changes response of AR to cause stimulation from antiandrogen
- **if progression under MAB occurs, antiandrogens (esp flutamide) should be stopped**

### What is the indication for MAB?

- **pts w/ sx due to local tumour extent or mets and ++ PSA or PAP levels**
  - more pronounced and faster effect of MAB on sx and markers

### What is PC-SPES?

- plant extract w/ estrogenic action, 5 $\alpha$ -reductase inhibition, and antimutagenic activity
  - contains estrogen and warfarin
- dose: 2 capsules of 230mg TID

### What are the s/e of PC-SPES?

- loss of libido
- ED
- painful gynecomastia
- reduction in body hair
- pitting edema
- DVT/PE
  - pt must be under antithrombotic measures
- CHF
- \$\$\$ expensive \$\$\$

### What are the effects of 5 $\alpha$ -reductase inhibition in pts w/ prostate cancer?

- delay of PSA rise by 9 months
- finasteride+flutamide vs. finasteride+Zoladex vs. flutamide+Zoladex: no difference
- preservation of libido and potency

### What is the usual time to progression and death of pts under endocrine tx for prostate cancer?

- metastatic disease: 50% pts w/ mets progress after 18-24mo and die after 30-36mo
- LN+ve disease only: median time to progression w/ early or delayed endocrine tx range from 20-60months

## Chapter 94 Questions - Hormone therapy.doc for prostate cancer

→ median time to death probably > 10 years (Messing 1999)

### What is the use of early vs. delayed hormonal tx in prostate cancer?

- EORTC studies
  - not relevant in pts w/ metastatic disease: all die too early to see a benefit of early hormones
- Messing (1999 NEJM): immediate vs. delayed hormones after RP in LN+ve pts
  - 98 men w/ LN +ve disease after RP randomized to immediate goserelin/orchiectomy or delay until disease progression
  - statistically significant survival advantage for immediate treatment in LN+ disease (77% vs. 18% disease-free survival)
  - criticized due to not reaching original sample size
  - **early endocrine tx delays progression**

### What studies have examined adjuvant treatment after RP in LN –ve disease?

- Bolla 1997 (EORTC study)
  - 415 pts randomized (208 to rads, 207 to rads + 3 yrs of LHRH agonist)
    - 50Gy to pelvis, 20Gy boost to prostate: 4 field box
    - 3.6mg goserelin qmo + 1mo of cyproterone initially to prevent flare
  - adjuvant rads vs. rads + LHRH agonist
    - significant difference in clinical DSS, cancer-specific survival, and OS
    - 5yr DSS (78% vs. 94%) and OS (62% vs. 79%) for rads alone vs. rads+LHRH
- RTOG trials
  - #1: 977 pts w/ T1-2, N+ or T3, Nx disease
    - immediate hormones + rads vs. delayed hormones + rads
    - small difference in OS (not significant)
    - significant difference for OS only in pts w/ Gleason 8-10 and +ve LN
  - #2: 456 pts w/ large T2b-4, N0-1 prostate cancer
    - radiation vs. neoadjuvant/adjuvant MAB + rads
    - significant improvement in local failure, distant mets, and biochemical control
- **adjuvant endocrine tx + rads for T3 and LN+ disease improves time to progression and DSS and OS**

### What is the role of intermittent androgen treatment for prostate cancer?

- advantage in recovery of libido and potency, avoids long-term s/e, potential for long-term survival by delaying progression to endocrine independence
- Akakura (1993)

### MTOPS and PCPT – who gets finasteride?

- MTOPS: doxazosin +/- finasteride, in prevention or delay of BPH
  - 3047 randomized, > 50 yrs, AUA score 8-30, Qmax 4-15 → average pts, w/ medium sized prostates
  - progression = sx increased by 4 pts, AUR, recurrent UTI, UI, or ARF
  - outcome: at 4 yrs, finasteride and doxazosin both worked, but combo doubled effect of tx (66% reduction in progression)
    - most progressed due to increase in AUA score, nobody got ARF
    - finasteride decreases prostate volume by 30%, decreased risk of AUR by 68% (81% in combination), decreased need for invasive therapy
    - high PSA > 4 or volume > 40cc, have 4X increase in benefit w/ combo
- PCPT: does finasteride decrease prevalence of biopsy-proven prostate cancer?
  - 18882 healthy men randomized to finasteride vs. placebo x 7 yrs → normal DRE/PSA, no severe BPH sx
  - assessed annually w/ DRE/PSA
  - all pts got bx at end of trial
  - outcome: > 9000 men included in analysis
    - 25% of men on biopsy had prostate cancer: higher than expected
    - 25% risk reduction of detecting prostate cancer on finasteride
      - ◆ in cancers that were found, 98% were small volume
    - of cancers found, 18% increase in pts w/ Gleason 7-10 in pts taking finasteride
  - What is worse: taking finasteride w/ lower risk of BPH/cancer but increased chance of higher grade prostate cancer?
    - Montreal Prostate Cancer Model: in all scenarios, finasteride increases survival
  - men w/ high risk of bothersome LUTs may benefit
  - men w/ high risk of prostate cancer: should not be placed on finasteride at this time

## **Chapter 94 Questions - Hormone therapy.doc for prostate cancer**

### **What is the definition of recurrence after RP?**

- Local
- Distant

### **What pts get antiandrogens as monotherapy vs. LHRH agonists?**

- advantages of pure antiandrogen as monotherapy:
  - elevation of plasma T and estradiol prevents serious side effects of castration and long-term use of LHRH agonist
  - less osteoporosis, spontaneous fracture, muscle wasting, anemia, fatigue

### **What is the natural hx of men with localized prostate cancer treated with hormones?**

- Albertsen (1995 JAMA): long term survival in men w/ localized prostate cancer treated conservatively
  - 450 men aged 65-75 w/ clinically localized prostate cancer treated w/ delayed or immediate hormones only
    - classified as either low-grade (Gleason 2-4), moderate-grade (Gleason 5-7) or high-grade (Gleason 8-10)
  - overall, 34% died of prostate cancer
  - cancer-specific mortality at 10 yrs / 15 yrs:
    - low-grade: 9% / 9% → minimal risk of dying of prostate cancer
    - moderate-grade: 24% / 28%
    - high-grade: 46% / 51%
  - Gleason score: most powerful predictor of survival





## **Chapter 95**

### **• Chemotherapy for Hormone-Resistant Prostate Cancer •**

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**How often does hormone-refractory prostate cancer occur in pts w/ androgen deprivation?**

- observed in the majority of pts w/i a predictable time
- median time to progression 12-18mo, median survival time 2-3 years

**Why does prostate cancer become hormone-refractory?**

- prostate cancer normally grows based on a cell proliferation rate that exceeds that of cell death
- androgen ablation affects cell death rate by inducing apoptosis
  - as tumour progresses, cell proliferation exceeds cell death due to accumulation of endocrine-independent cells that eventually increase in # and dominate the biologic scenario

**Which growth factors can be induced by androgens?**

- EGF, IGF, FGF, TGF-alpha and beta, PDGF, NGF

**What is the first manifestation of disease progression in pts w/ hormone-resistant prostate cancer (HRPC)?**

- increasing PSA

**What is the time interval b/w PSA increase and radiologic evidence of mets after androgen deprivation?**

- 6 months

**Why does HRPC usually metastasize to bone?**

- not fully known
  - circulating HRPC cells arrest in cortical and medullary bone spaces
  - adhere to bone surfaces via receptors for integrins, collagens, laminins
  - cell growth promoted by growth factors

**How often does one see involvement of visceral sites in HRPC?**

- relatively uncommon, even in widespread disease
- visceral mets in < 10% pts
  - lung 5.5%
  - liver 6.5%
- 20% have soft tissue/nodal disease

**What is the most common hematologic abnormality in HRPC?**

- anemia → treat w/ transfusions prn
  - EPO not successful: decreased bone marrow reserve

**What are the causes of anemia seen in HRPC?**

- anemia of chronic disease
- bone marrow invasion
- blood loss
- microangiopathic hemolytic anemia
  - associated w/ DIC
- previous tx w/ radiation
- systemic use of radiopharmaceuticals
- long-term androgen deprivation
- systemic chemotherapy
- extensive bone marrow involvement by tumour

**What are the complications of HRPC?**

- Bone mets

## Chapter 95 Questions - HRPC.doc

- pain, compression, pathologic fractures
- Hematologic
  - anemia
  - granulocytopenia
  - thrombocytosis
  - thrombocytopenia
  - thrombotic complications
- Urologic
  - obstructive uropathy: stent or NT placement
- Neurologic
  - epidural cord compression
  - back pain

### What is the treatment of cord compression from HRPC?

- high-dose IV steroid: dexamethasone 4-100mg
- external-beam radiation
- surgical decompression w/ spinal stabilization

### How does one evaluate and treat the pt w/ HRPC?

- PSA
- serum T: ensure at castrate levels
- discontinue all antiandrogens (steroidal and nonsteroidal)
  - measure serial PSA x 4-8 weeks before next manoeuvre
  - poorly differentiated, anaplastic, or neuroendocrine tumours unlikely to respond to androgen deprivation
- 2<sup>nd</sup> line endocrine manipulation
  - DES
  - PC-SPES
  - aminoglutethamide
  - ketoconazole
  - corticosteroids
  - withdrawal of antiandrogens
- cytotoxic chemotherapy
  - continue gonadal androgen suppression during chemo

### How does a rising PSA relate to disease progression?

- increasing PSA precedes other evidence of advancing disease by 6 months

### How can one determine if pt non-compliance is an issue in a pt w/ a rising PSA?

- measure serum T

### What prognostic factors are important in pts w/ HRPC?

- Definite
  - performance status
  - baseline hemoglobin
- Probable (not a factor in RCT)
  - liver involvement
  - baseline PAP, ALP, LDH
  - time from initiation of androgen deprivation to initiation of chemotherapy
  - response to therapy
  - baseline PSA
  - >50% decline in post-tx PSA for > 4 weeks
- Equivocal (more data needed)
  - extent of disease on bone scan
  - continuation of androgen deprivation

### What single-agent chemotherapeutic agents have been used to treat HRPC, and with what success?

- cyclophosphamide: 30% RR, decrease in PSA, measurable response also seen
- paclitaxel: poor RR, measurable decrease in PSA
- mitoxantrone: modest subjective benefits
- docetaxel: 30-50% RR, 50% decline in PSA

## **Chapter 95 Questions - HRPC.doc**

- vinorelbine tartrate: 40% RR, 50% decline in PSA
- estramustine: 21% RR, >50% decline in PSA
- fluorouracil: none
- etoposide: 8% RR, 1 pt had > 50% decline in PSA, 1 pts had measurable response
- carboplatin: 12% RR, some PSA decline and measurable response
- losoxantrone: 25% RR, 60% had subjective improvements

### **What are the common toxicities for the following cytotoxic chemotherapeutic agents?**

- cyclophosphamide: N/V, heme
- paclitaxel: heme, CVS, anaphylaxis
- mitoxantrone: heme
- docetaxel: fatigue, stomatitis, edema, heme
- vinorelbine tartrate: neutropenia
- estramustine: N/V, heme, thromboembolic, gynecomastia
- fluorouracil: heme, mucositis
- etoposide: heme
- carboplatin: heme
- losoxantrone: heme

### **Why are clinical trials difficult to perform in pts w/ metastatic prostate cancer?**

- related to pattern of spread
  - diffuse osteoblastic pattern of bone mets difficult to reliably measure

### **What is the antiandrogen withdrawal syndrome?**

- characterized by decrease in PSA and reduction of measurable tumour after d/c antiandrogens
  - may be evidence of disease improvement (short duration: 3 months)
  - may be enhanced by use of steroids

### **What combinations of medications have been used to treat HRPC, and what are their results?**

- mitoxantrone + prednisone vs. prednisone alone
  - improvement in QOL, no change in OS
- estramustine phosphate + vinblastine
- estramustine phosphate + paclitaxel (Taxol)
  - 10/17 > 50% decline in PSA
- estramustine phosphate + docetaxel (Taxotere)
  - 23/35 > 50% decline in PSA, 77% 1 year survival
- estramustine phosphate + etoposide
- suramin + hydrocortisone
  - 30% had > 50% decrease in PSA
  - not recommended for treatment
- **none of the chemotherapeutic regimens tested superior to another wrt OS**

### **What is suramin?**

- polysulfonated naphthylurea
- multiple biologic functions
- used previously for AIDS, parasitic disorders
- not recommended by FDA: modest palliative benefits in symptomatic end-stage disease

### **What are the side effects of suramin?**

- neurotoxicity
- renal toxicity
- syndrome of malaise-fatigue and anorexia

### **What is the role of radiation in pts w/ HRPC?**

- used for pts w/ bulky disease or brain mets

### **What is the most debilitating sx associated w/ metastatic prostate cancer?**

- cancer-related pain

### **What are the characteristics of neuroendocrine differentiation of prostate cancer?**

## Chapter 95 Questions - HRPC.doc

- inherent endocrine resistant disease
  - expression of R to various neuroendocrine peptide growth factors
  - frequent visceral involvement
  - rapidly growing soft tissue mets
  - rapidly growing mass at primary site
  - bulky retroperitoneal masses
  - rapid development of visceral mets
  - lytic bone mets
  - high incidence of brain involvement
  - stop expressing PSA

### Why is hypercalcemia rare in metastatic prostate cancer?

- bone mets are predominantly blastic
- lack of significant osteoclastic activity

### What are the various pain syndromes in metastatic HRPC and their respective treatments?

- focal bone pain
  - pharmacologic
  - localized radiation
  - surgical stabilization of pathologic fractures
- diffuse bone pain
  - pharmacologic
    - narcotics, corticosteroids, bisphosphonates, NSAIDs
  - radiopharmaceuticals ( $^{32}\text{P}$ ,  $^{89}\text{Sr}$ )
  - wide field radiation
- epidural mets and cord compression
  - dexamethasone 10mg IV (loading dose) then 4 mg q6hrs: taper over 2-3 weeks
  - radiotherapy
  - surgical decompression and stabilization
- plexopathies (from direct tumour invasion)
  - pharmacologic
    - narcotic, TCA, anticonvulsants
  - radiation
  - nerve blocks
- miscellaneous neurogenic causes: postherpetic neuralgia, peripheral neuropathy
  - pharmacologic
  - d/c neurotoxic drugs (taxol, alkaloids, platinum, suramin)
- uncommon pain syndromes: skull mets w/ CN involvement, painful liver mets or pelvic masses
  - radiation
  - pharmacologic
  - steroids
  - chemotherapy

### What are the symptoms of cord compression from epidural mets?

- radicular back pain
- motor weakness
- sensory changes
- bladder/bowel dysfunction

### What new systemic approaches are being developed for HRPC?

- MMP inhibitors: marimastat, AG-3340
- inhibition of angiogenesis: TNP-470, CM-101, thalidomide, tecogalan, angiostatin, endostatin, anti-VEGF Ab, suramin
- differentiation tx: retinoids, vitamin D derivatives, butyrates
- inhibition of signal transduction and cell-cell interaction mechanisms
- anti-sense compounds: synthetic oligonucleotides
- tumour vaccines and gene therapy:
- endothelin antagonists: analgesic properties, suppress development of osteoblastic activity
  - atrasentan 2.5 or 10mg PO OD

### What studies show that taxotere improves survival in men with HRPC?



## Chapter 95 Questions - HRPC.doc

- TAX 327: 1006 pts w/ metastatic HRPC
  - 1 of 3 treatment arms
    - Taxotere 75mg/m<sup>2</sup> once every three weeks plus daily prednisone
    - Taxotere 30 mg/m<sup>2</sup> every week for five out of six weeks plus daily prednisone
    - mitoxantrone 12mg/m<sup>2</sup> every three weeks plus daily prednisone (established standard of care)
  - average life expectancy for HRPC: 6-12mo
  - decreased risk of death by 24%
  - 43% more patients on Taxotere (vs. mitoxantrone) had a sustained decrease in PSA of > 50 percent
  - 59% more patients on Taxotere reported a sustained, reduced level of pain or requirement for analgesics
- SWOG 9916
  - decreased risk of death by 20%
  - 27% increase in progression free survival
  - significant increase in PSA response (50 % versus 27%)
  - 55% increase in objective response rate (17% versus 11% complete or partial regression of tumour lasting > four weeks)

### Recommendations:

#### Chemotherapy for Androgen Independent Prostate Cancer – AUA Update XXII #3

#### What was designated as a partial response to therapy by the NCI in trials for HRPC?

- 1999 consensus statement
  - PSA decrease of > 50% for > 4 weeks

#### What is the role of continued hormonal therapy in the context of HRPC?

- conflicting reports
  - retrospective analysis by SWOG: no improvement in survival for pts remaining on therapy
  - ECOG analysis: slight survival benefit
- testicular androgen suppression continued throughout any further treatment

#### What are the effects of bisphosphonates in bony mets in HRPC?

- inhibit adhesion of tumour cells to the bony matrix
- prevent tumour cell invasion into the bony matrix
- inhibit matrix metalloproteinases

#### What are the clinical effects of zoledronic acid on HRPC?

- RCT of 422 pts tx w/ IV zoledronic acid q3weeks
  - decreased skeletal-related events and pathologic fractures
  - decreased time to first skeletal event, vertebral #, and pathologic #
  - improved pain control
  - minimal toxicity
- should be used as part of standard therapy for all men w/ HRPC and documented bony mets

#### What are the NCCN guidelines for standard of care for HRPC?

- National Comprehensive Cancer Network 2000 guidelines
  - supportive care
  - 2<sup>nd</sup> line hormonal therapy
  - combination chemo if performance status adequate
  - local radiation therapy for specific painful or problematic disease areas
  - systemic radiotherapy w/ samarium or strontium
  - therapy on a clinical trial is encouraged

#### What phase III trials have been performed using chemotherapy to treat HRPC in the past decade?

- Prednisone vs. Mitoxantrone + Prednisone (Tannock IF – J Clin Oncol 1996)
  - 161 pts, primary endpoint: palliative response
  - 38% of MP pts and 21% of P pts met criteria for primary response
  - time to disease progression longer in MP group, **no difference in overall survival**
    - increase in survival for pts w/ >50% decrease in PSA
- Hydrocortisone vs. Mitoxantrone + Hydrocortisone (Kantoff PW – J Clin Oncol 1999)
  - 242 pts, primary endpoint: 50% increase in survival
  - **no difference in overall survival** despite appropriate power

## Chapter 95 Questions - HRPC.doc

- increase in survival for pts w/ >50% decrease in PSA
  - modest benefit in time to disease progression and time to tx failure in MH group (3.7 vs. 2.3 months)
- Vinblastine vs. Estramustine + Vinblastine (Hudes G – J Clin Oncol 1999)
  - 201 pts, primary endpoint: overall survival
  - no difference in OS b/w 2 groups, but only powered to detect > 50% increase
  - 25% pts in each arm d/c'd tx before completing 1 8-week tx cycle
  - EV pts had better time to progression
- Hydrocortisone + Placebo vs. Hydrocortisone + Suramin (Small EJ – J Clin Oncol 2000)
  - 460 pts, primary endpoint: reduction of pain and opiate requirements
  - HS had greater overall decrease in pain score and opioid use, minor +ve effect in time to disease progression and % of pts achieving > 50% reduction in PSA
  - OS no different, median OS < 10months (pt population w/ advanced disease)

### What is mitoxantrone and how does it act?

- anthracycline antibiotic – 12mg/m<sup>2</sup> q3wk
- causes cytotoxicity by direct DNA damage

### What are the s/e of mitoxantrone?

- heme: myelosuppression – neutropenia, anemia, thrombocytopenia
- cardiotoxicity – decreased EF, CHF
- N/V

### What are the 2 common taxanes and how do they work?

- paclitaxel (Taxol) and docetaxel (Taxotere)
- act via inhibition of microtubule disassembly in dividing cells

### What are the most common side effects of taxane therapy?

- myelosuppression
- edema
- asthenia
- peripheral neuropathy
- allergic reaction
- alopecia

### What results have been seen in pts treated w/ taxanes for HRPC?

- Paclitaxel
  - phase II ECOG trial: 23 pts w/ measurable disease – 1 pt had PR, 4 pts had small reductions in PSA
  - Trivedi (Cancer, 2000): 18 pts w/ bone or visceral mets – 4 pts had major response, 1 CR
- Docetaxel
  - Friedland (Sem Oncol, 1999): 21 pts – 7 pts had decrease in PSA by > 50%, 6 pts had response on CT or bone scan
  - Picus (Sem Oncol, 1999): 35 pts – 16 pts had decrease in PSA by > 50%, 7 pts had response on CT or bone scan
  - Berry (Sem Oncol, 2001): 60 pts in multicenter study – 41% had PSA response, associated w/ improvement/stabilization of performance status, median OS 9.4months

### What is estramustine, and how does it work?

- conjugate of 17-beta estradiol w/ the alkylating agent nor-nitrogen mustard
- cytotoxic effects due to binding of tubulin and microtubule associated proteins, promoting tubule disassembly and interruption of mitosis

### What are the s/e of estramustine?

- GI
- cardiac
- **thromboembolic events: 5-10% incidence, most life-threatening risk of therapy**
  - risk not decreased w/ ASA or Coumadin
- must avoid taking Ca-containing foods and antacids when taking the drug, due to poor absorption
- hypocalcemia
- HUS
- myelodysplastic syndrome
- AML

## **Chapter 95 Questions - HRPC.doc**

### **What are the results of phase II studies that look at the combination of estramustine and docetaxel?**

- Savarese (J Clin Oncol, 2001): 47 pts, 68% PSA response, of these → 3 pts CR and 9 pts PR on imaging, median survival 20mo
- Sinibaldi (Proc Am Soc Clin Oncol, 2000): 32 pts, 45% PSA response, of these → 3 pts PR on imaging
- Petrylak (Proc Am Soc Clin Oncol, 2000): 35 pts, 74% PSA response, 4 pts PR on imaging
- Natale (Proc Am Soc Clin Oncol, 1999): 18 pts, 78% PSA response, 4 pts PR on imaging

### **What phase III studies are being performed that look at taxane therapy in HRPC?**

- SWOG study: phase III trial of Mitoxantrone + Prednisone vs. Estramustine + Docetaxel  
→ powered to determine if survival benefit exists w/ taxane therapy, and comparison of palliative benefit

### **How do pts treated w/ multiple previous hormonal or chemotherapy regimens react to chemotherapy?**

- in general, extensive pretreatment translates into higher incidence of s/e and lower probability of response  
→ does not apply to any individual pt

### **How does one measure performance status?**

- ECOG performance status score (Eastern Cooperative Oncology Group)
  - Grade 0: Fully active, able to carry on all pre-disease performance without restriction
  - Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light house work, office work)
  - Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
  - Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
  - Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
  - Grade 5: Dead

### **Docetaxel + Estramustine vs. Mitoxantrone + Prednisone: NEJM 2004 (Petrylak)**

- 770 men w/ metastatic HRPC, 674 eligible: 338 pts to get DE, 336 to get MP
  - primary endpoint: OS
  - secondary endpoint: progression-free survival, RR, PSA decline of > 50%
- intention-to-treat analysis
- OS longer in DE vs. MP (17.5mo vs. 15.6mo)
- longer time to progression in DE: 6.3mo DE, 3.2mo MP
- more PSA decline in DE: 50% DE, 27% MP
- more complications in DE group: neutropenic fevers, N/V, CVS events
  - pain decline same for both groups





## Chapter 96

### • Urinary Lithiasis: Etiology, Diagnosis, Medical Management •

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#### What is the prevalence and recurrence rate of kidney stones?

- prevalence 2-3%
- recurrence rate w/o tx 10% at 1yr, 35% at 5yr, 50% at 10yr

#### What factors affect the chance of developing kidney stones?

- Intrinsic factors
  - genetics: FHx and race
    - rare in Natives, blacks, Israelis
    - common in Asians and whites
    - FHx: 25% have +ve FHx
  - age
    - peak incidence in 40s
    - onset often in teens
  - male sex
    - 3:1 male:female
      - ◆ difference in inhibitor excretion may explain the sex differences
- Extrinsic factors
  - geography
    - more stones in mountainous, desert, or tropical areas
    - increased incidence: US, UK, Scandinavia, Mediterranean, northern India/Pakistan, northern Australia, central Europe, Malayan peninsula, China
    - decreased incidence: Central and South America, Africa, aboriginal Australia
    - more stones on Eastern US
  - climate and seasonal factors
    - incidence highest in July, Aug, Sep: 1-2 months after maximal mean annual temperature
    - dehydration, increased exposure to sunlight and increased vitamin D production w/ increased urinary Ca excretion
  - water intake: decreases average time of residence of free crystal particles in urine and dilutes components
  - diet
    - excessive amounts of purine, oxalates, Ca, P, other elements
    - Worcestershire sauce, milk products (cheese, ice cream), vegetarian diet (more childhood stones)
    - **prevalence of stone disease lowest in pts on high-calcium diet**
  - occupation
    - stones more likely to be found in pts w/ sedentary lifestyles
    - professional and managerial groups, affluent countries/regions/societies, spaceflight
      - ◆ more disposable income to spend on animal protein → increased urinary conc of Ca, oxalate, uric acid
  - medical conditions
    - MSK, granulomatous diseases, GI (IBD, bowel OR), meds, hypercalcemia, RTA
  - stress
    - lower family income, mortgage problems, emotional life events associated w/ stone disease

#### What theories can explain the increased incidence of stones in men vs. women?

- lower serum T levels may contribute to the protection women and children have against oxalate stones
  - androgens increase while estrogens decrease urinary oxalate excretion, plasma oxalate concentration, and kidney calcium oxalate crystal deposition
- increased urinary citrate concentrations in the urine of women

#### What hereditary disorders cause renal stones?

- RTA: nephrocalcinosis and nephrolithiasis in 70%
- cystinuria

## Chapter 96 Questions - Stones.doc

- xanthinuria
- dihydroxyadeninuria
- Dent's disease
- X-linked recessive nephrolithiasis
- X-linked recessive hypophosphatemic rickets

### What is the $K_{sp}$ ?

- thermodynamic solubility product
- constant: equal to product of concentrations of the pure chemical components at which the solid and solvent stages are in equilibrium
- $K_{sp}$  for Ca oxalate monohydrate in distilled water =  $2.34 \times 10^{-9}$

### What is the formation product?

- the point at which a solution becomes unstable
  - inhibitors generally not effective above this level of concentration, and nucleation will occur
  - due to inhibitors and other molecules, Ca oxalate precipitation occurs w/ supersaturation 7-11X its solubility

### What is the difference b/w nucleation and aggregation?

- nucleation: formation of earliest crystal structure that will not dissolve and has the form of a lattice that is characteristic of that crystal
- aggregation: crystal nuclei clump together → can occur within 60sec

### What is meant by homogenous or heterogenous nucleation?

- homogenous nucleation = process by which nuclei form in pure solutions
- heterogenous nucleation = crystal nuclei formation on existing surfaces
  - ex: epithelial cells, cell debris, urinary casts, other crystals, RBC
  - epithelial cell injury lowers the concentration at which crystals form

### What is the time taken for urine to pass from the glomerulus through the nephron into the collecting system?

- 2-5 minutes

### Where is the point of greatest supersaturation of urine?

- renal papilla

### What are the causes of increased crystal retention?

- anatomic abnormalities
  - MSK, UPJO
- increased stickiness of tubular epithelium
- abnormalities of renal cellular calcium or oxalate transport

### What are the inhibitors of stone formation?

- Calcium Phosphate stones
  - citrate → most potent complexor of calcium
  - nephrocalcin: made in PCT and thick ascending limb
  - pyrophosphate
  - magnesium
- Calcium Oxalate stones
  - citrate
  - nephrocalcin
  - pyrophosphate
  - RNA fragments
  - GAG
  - uropontin: aspartic acid rich protein
    - inhibits nucleation, growth, and aggregation
  - sodium
- Calcium Oxalate Monohydrate
  - nephrocalcin → most potent inhibitor of COM in simple solutions
  - Tamm-Horsfall glycoprotein → **inhibits calcium oxalate aggregation only, does not affect nucleation/growth**
    - made in thick ascending limb and DCT
- Uric acid

## Chapter 96 Questions - Stones.doc

- none
- Others
  - urinary prothrombin fragment 1 → **most potent inhibitor identified in normal urine**
  - bikunin (light chain of inter-alpha inhibitor) → inhibits crystal nucleation and aggregation

### What are the organic inhibitors of stone formation?

- GTAMPPONSSSS – organic inhibitors of stone formation
- GAG, TH, albumin, macroglobulin, pyrophosphate, pontium (uro), O, nephrocalcin, nucleic acid (RNA), SSSS

### Which inhibitors prevent stone nucleation, growth, or aggregation?

- Nucleation: nephrocalcin, bikunin, uropontin
- Growth: nephrocalcin, uropontin
- Aggregation: Mg, citrate, nephrocalcin, TH glycoprotein, bikunin, uropontin, GAG

### Where is nephrocalcin synthesized?

- PCT and thick ascending limb

### Where is Tamm-Horsfall glycoprotein made?

- thick ascending limb and DCT

### What inhibitors act as complexors of Ca?

- citrate → most potent complexor of Ca
- Mg

### What inhibitors can act as promoters of crystal formation?

- GAG: promote crystal nucleation, but inhibit crystal aggregation and growth
- TH protein: can act as an inhibitor or promoter

### What is the matrix?

- non-crystalline protein in stones
  - most stones have matrix content of 3% by weight
  - matrix stones are 65% matrix by weight → esp in association w/ UTI
- derivative of several of the mucoproteins of urine and serum: TH, uropontin
  - 65% hexosamine, 10% bound water
  - substance A: 3-4 Ag found in all matrix stones
- *E. Coli* may increase matrix formation

### What other proteins are incorporated into stones?

- albumin, globulin, TH protein, nephrocalcin, alpha<sub>1</sub> and beta<sub>2</sub> microglobulin, hemoglobin, neutrophil elastase, AAT, protectin, alpha<sub>1</sub> acid glycoprotein, apolipoprotein A1, etc...

### How can non-urease producing bacteria like *E. Coli* play a role in stone formation?

- by increasing the production of urinary matrix

### How does Ca absorption occur in the gut?

- 30-45% of PO Ca is absorbed: greater on low-Ca diets
- mediated through cellular and pericellular pathways
  - if high luminal concentration: diffusion
  - if low concentrations: cellular pathways
- occurs in ionic state
- **Ca<sup>2+</sup> maximally absorbed in jejunum and proximal ileum where pH < 6**
- when dietary Ca low, production of vit D are high, stimulating Ca absorption
- vit D is most important factor that increases active Ca absorption

### How does vitamin D affect calcium absorption?

- 1,25-D increases calcium absorption by brush border membranes of intestinal mucosa
  - low Ca levels stimulate vitamin D production
- most potent stimulator of intestinal Ca absorption

### How is vitamin D manufactured?

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- sunlight converts 7-dehydrocholesterol in the skin to previtamin D3
- transported to the liver and hydroxylated to 25-hydroxyvitamin D3
- transported to kidney, hydroxylated in PCT by 1 $\alpha$ -hydroxylase to 1,25-dihydroxyvitamin D3 → stimulated by PTH
- also manufactured by macrophages

### How does PTH stimulate 1,25-D creation?

- PTH stimulates 1 $\alpha$ -hydroxylase in mitochondria of PCT
- calcitriol secreted into blood, transported to intestine, and binds to R in brush border  
→ PTH also stimulates osteoclasts to demineralize bones by breaking down apatite → releases Ca into serum

### What are the effects of 1,25-D on bone and kidney?

- stimulates bone resorption of Ca by increasing osteoclast activity, in concert w/ PTH
- stimulates renal resorption of Ca

### How does 1,25-D affect P absorption?

- increases absorption in duodenum and jejunum through active transport  
→ 60% of P in diet absorbed by intestine  
→ 65% of R excreted by kidney, rest by intestine

### How does Mg affect PTH excretion?

- Mg inhibits PTH excretion  
→ 95% of filtered Mg reabsorbed by kidney, mostly in loop of Henle

### What foods have the highest oxalate content?

- leaf tea, powdered coffee
- spinach, rhubarb

### How well is oxalate absorbed by gut?

- poorly absorbed from intestine  
→ stomach and distal bowel may be primary sites of absorption
- increased in pts w/ small bowel resection or IBD if colon present
- **increased in pts w/ increased intestinal Ca absorption**

### How is oxalate degraded in the gut?

- 50% of ingested oxalate destroyed by bacterial action
- fecal bacteria *Oxalobacter formigenes* and *Pseudomonas oxalaticus* contain enzymes that degrade oxalate

### How is oxalate handled by the kidney?

- freely filtered at the glomerulus
- secreted along entire length of PCT

### Why do pts w/ CF often get oxalate stones?

- undergo long treatment periods of antibiotics
- lack *O. formigenes* (degrades oxalate) in intestine, and exhibit hyperoxaluria

### What are the sources of urinary oxalate?

- 85% endogenous production in liver: 40% ascorbic acid, 40% glycine  
→ ascorbic acid undergoes enzymatic and nonenzymatic conversion to oxalate
- 15% dietary sources: oxalate rich foods, meat protein (tryptophan, hydroxyproline)

### How does the kidney handle acid?

- kidney excretes entire H<sup>+</sup> load produced by the body and reclaims all the bicarbonate that is filtered
- proximal nephron reabsorbs bicarb through secretion of H<sup>+</sup> into lumen  
→ Na-K-ATPase on basolateral membrane creates decrease in intracellular sodium  
→ protons produced in tubular cell by carbonic anhydrase  
➤ carbonic acid → bicarb + protons  
→ **80% of filtered bicarb reabsorbed by PCT, rest by distal nephron**  
→ distal nephron can generate 1000-1 H<sup>+</sup> gradient b/w cell and tubular lumen

### How does the kidney handle citrate?



## Chapter 96 Questions - Stones.doc

- 75% of filtered citrate is reabsorbed, rest is excreted  
→ most in PCT

### What factors determine citrate excretion?

- Reduced excretion
  - acid-base status of body
    - absorbed citrate is oxidized, creating alkali
      - ◆ raises pH and bicarb concentration in renal tubular cell and inhibits tubular reabsorption of citrate
    - acidosis: reduces citrate excretion by inhibiting efflux of citrate from mitochondria
    - hypokalemia, high-protein diet, exercise: intracellular acidosis, decreasing excretion
  - androgens: decrease excretion
- Increased excretion
  - pregnancy: increases excretion
  - PTH, calcitonin, vit D: increase excretion

### Classify the different types of cystinuria.

- Type 1: total loss of intestinal transport of cystine, lysine, arginine
- Type 2: some cystine uptake in jejunum
- Type 3: reduced uptake by jejunal mucosa, as well as after PO cystine load

### What are the sources of cystine?

- absorbed from gut from diet
- converted from methionine
- reabsorbed in PCT

### What is the mutant gene in cystinuria?

- AR disorder of transmembrane cystine transport in intestine and kidney → only homozygotes form stones
- codes for an abnormal transport system involving cystine, ornithine, lysine, arginine (COLA)
  - ornithine, lysine, and arginine freely soluble → do not form stones
- secretion and paracellular leakage of cystine are normal, but impaired reabsorption across brush border in kidney
  - decreased cystine absorption in intestine
  - decreased cystine resorption in PCT

### What are the causes of Ca stone formation?

- Hypercalciuria
  - Absorptive – increased intestinal absorption of Ca, leading to increased renal filtration of Ca
    - Type 1: hyperabsorption of Ca regardless of vit D
    - Type 2: increased absorption of Ca while on regular diet, normal Ca excretion if on low-Ca, low-Na diet
    - Type 3: low serum phosphate, causing increased vit D levels which increase Ca absorption
  - Renal – primary renal leak of Ca
  - Resorptive – increased bone demineralization from excessive PTH levels and increased intestinal absorption of Ca
  - Idiopathic – increased urinary Ca w/ normal serum Ca: seen in 30-60% of pts w/ Ca oxalate stones
- Hypercalcemia
  - primary hyperparathyroidism: > 85% → most common cause of hypercalcemia in an outpt setting
  - malignancy-associated hypercalcemia → most common cause of hypercalcemia in an inpt setting
  - sarcoid
  - hyperthyroidism: 5-10% pts get hypercalcemia
  - glucocorticoid-induced hypercalcemia
  - pheochromocytoma
  - familial hypocalciuric hypercalcemia: AD disorder of hypercalcemia
  - immobilization: causes increased bone turnover
  - iatrogenic
    - thiazide diuretics: increase PCT reabsorption of Ca → may unmask primary hyperparathyroidism
    - Li
    - estrogen and antiestrogen in pts w/ skeletal mets from breast ca
  - milk-alkali syndrome
  - ++ vitamin D ingestion
  - vitamin A toxicity
- Hyperoxaluria
  - increased oxalate production by liver

## Chapter 96 Questions - Stones.doc

- primary hyperoxaluria
  - ◆ Type 1: AR inborn error of metabolism – defect in enzyme AGT in liver (normally changes glyoxylate → glycine)
  - ◆ Type 2 (L-glyceric aciduria): deficiency of liver enzyme D-glycerate dehydrogenase and glyoxalate reductase –
- increased hepatic conversion
  - ◆ pyridoxine deficiency
  - ◆ ethylene glycol ingestion: converted to glycolic acid and glycoaldehyde
  - ◆ methoxyflurane anaesthesia
- increased oxalate absorption (enteric hyperoxaluria): malabsorption
- hyperoxaluria in idiopathic calcium oxalate stone disease
- Hypocitraturia (mnemonic: AMEN To Da PACE)
  - **Acidosis most important factor**
    - **distal RTA, other causes of acidosis: AG vs. non**
  - Mg decrease: hypomagnesuria
  - Enalapril
  - Na intake increase
  - Thiazide-induced hypocitraturia: intracellular acidosis
  - Diarrhea: intestinal alkali loss causes metabolic acidosis
  - Protein increases in diet
  - Active UTI
  - Citrate malabsorption
  - Exercise
- Hypomagnesuria
  - IBD, malabsorption
- Sex hormones
  - testosterone
- Nanobacteria
- RTA

### Classify the different types of hypercalciuria.

- Absorptive – increased intestinal absorption of Ca, leading to increased renal filtration of Ca
  - Type 1: hyperabsorption of Ca regardless of vit D
    - some pts have increased vit D levels causing increased absorption of Ca by intestine
    - these pts typically do have increased vit D levels anyways
  - Type 2: increased absorption of Ca while on regular diet, normal Ca excretion if on low-Ca, low-Na diet
  - Type 3: low serum phosphate, causing increased vit D levels which increase Ca absorption
- Renal – primary renal leak of Ca
  - increased PTH levels, which stimulate vit D production
- Resorptive – increased bone demineralization from excessive PTH levels and increased intestinal absorption of Ca
- Idiopathic – increased urinary Ca w/ normal serum Ca: seen in 30-60% of pts w/ Ca oxalate stones
  - may be inherited as AD trait
    - seen in some ppl w/ pseudoxanthoma elasticum or CF
  - occurs in 5-10% of healthy people, present in 50% of people w/ Ca stones

### What is the definition of hypercalciuria?

- Pak: most stringent definition
  - excretion of > 200mg Ca/24h after 1 weeks adherence to 400mg Ca, 100mEq sodium diet
- excretion of > 4mg Ca / kg body weight / day
- excretion of > 7mmol in men, 6 mmol in women

### What 2 factors distinguish renal from absorptive hypercalciuria?

- elevated fasting urinary Ca levels
- increased PTH

What are the potential causes of the renal Ca leak in renal hypercalciuria?

- not known
  - UTIs
  - high serum osteocalcin
  - low urinary citrate excretion

## Chapter 96 Questions - Stones.doc

- primary structural abnormalities – tubular ectasia
- functional defect in PCT
- abnormal tubular function
- excessive dietary intake of Na
- PGs

### How can one determine b/w the types of hypercalciuria?

- Calcium Load test
  - 7d of low-Ca, low-Na diet
  - fast x 12h from 9pm
  - 7am next day empty bladder → discard
  - drink 600cc water
  - urine collected from 7-9am = fasting sample
  - 9am: 1g Ca orally
  - urine collected from 9-1pm = post Ca load sample
  - measure for Ca, Cr, cAMP
- absorptive: fasting ( $U_{Ca} < 0.11$ ,  $U_{cAMP} < 6.85$ ), load ( $U_{Ca} > 0.2$ ,  $U_{cAMP} < 4.6$ )
- renal: ( $U_{Ca} > 0.11$ ,  $U_{cAMP} > 6.85$ ), load ( $U_{Ca} > 0.2$ ,  $U_{cAMP} < 6.85$ )
- primary hyperparathyroidism: ( $U_{Ca} > 0.11$ ,  $U_{cAMP} > 6.85$ ), load ( $U_{Ca} > 0.2$ ,  $U_{cAMP} < 6.85$ )

### What are the causes of hypercalcemic nephrolithiasis?

- primary hyperparathyroidism: > 85% → most common cause of hypercalcemia in an outpt setting
  - dx requires demonstration of hypercalcemia in absence of any other d/o that increases serum Ca
    - PTH elevated in > 90% of pts w/ surgically proved primary hyperparathyroidism
  - suspect in pts w/ renal stones w/ elevated serum Ca
- malignancy-associated hypercalcemia → most common cause of hypercalcemia in an inpt setting
- sarcoid
  - other granulomatous diseases: TB, histoplasmosis, coccidiomycosis, leprosy, silicosis
- hyperthyroidism: 5-10% pts get hypercalcemia
- glucocorticoid-induced hypercalcemia
- pheochromocytoma
- familial hypocalciuric hypercalcemia: AD disorder of hypercalcemia
  - do not treat
- immobilization: causes increased bone turnover
- iatrogenic
  - thiazide diuretics: increase PCT reabsorption of Ca → may unmask primary hyperparathyroidism
  - Li
  - estrogen and antiestrogen in pts w/ skeletal mets from breast ca
- milk-alkali syndrome
- ++ vitamin D ingestion
- vitamin A toxicity

### What is the tx of primary hyperparathyroidism?

- stone formers: surgical removal of parathyroid adenoma
- asymptomatic: controversial
  - no treatment if no sx
    - many pts have nonspecific sx when questioned: malaise, fatigue, abdo pain, bone pain, constipation, depression
  - estrogen tx: inhibits action of PTH on bone

### What is the most common cause of hypercalcemia in an inpt setting?

- malignancy
  - lung and breast ca: 60%
  - RCC: 10-15%
  - H&N ca: 10%
  - hematologic: 10%
  - rarely seen in prostate ca

### What is the cause of stones in malignancy?

- due to production of PTH-related polypeptide by tumour
  - humoral hypercalcemia of malignancy

## Chapter 96 Questions - Stones.doc

- secretion of cytokines (**osteoclast activating factors**) that act locally in the bone marrow to stimulate osteoclastic bone resorption: esp MM
  - PGE, TNF, IL-1, TGF

### What is sarcoid, and how does it cause hypercalcemia?

- sarcoidosis is a multisystem granulomatous disorder of unknown etiology
  - most commonly affects young adults
  - bilateral l/a, pulmonary infiltration, and **skin and eye lesions**
- sarcoid **granuloma makes 1,25-D**, increasing intestinal Ca absorption, hypercalcemia, hypercalciuria
  - most ppl w/ sarcoid have low PTH
- start these pts on steroids → watch Ca level fall in response to short term steroid administration
  - steroids inhibit intestinal absorption, causing hypocalcemia and hypocalciuria

### How does hyperthyroidism cause hypercalcemia?

- stimulation of bone resorption by thyroxine and tri-iodothyronine

### How do steroids affect calcium levels?

- actions on bone: increase serum Ca
  - increased bone resorption, decreased bone formation, osteopenia
- actions on intestine: decrease serum Ca
  - inhibits intestinal absorption → reduces serum Ca and urinary Ca excretion
- stimulates parathyroids: increase serum Ca

### How do pts w/ pheo develop hypercalcemia?

- usually in pts w/ MEN 2
- catecholamines stimulate secretion of PTH
- may stimulate osteoclasts

### What is the treatment of hypercalcemia?

- IV fluids – volume expansion
- d/c thiazides
- loop diuretic: promotes Ca excretion
- bisphosphonates: inhibit osteoclasts
  - pamidronate 30-90mg IV
  - zoledronate 4mg IV in 15min
- calcitonin: inhibits osteoclasts
- mithramycin
  - replaced due to s/e: soft tissue irritation, LFT changes, nephrotoxic, thrombocytopenia
- glucocorticoids
- gallium nitrate: nephrotoxic
- IV phosphate: not used as can cause soft tissue calcification

### Classify the types of hyperoxaluria.

- increased oxalate production by liver
  - primary hyperoxaluria
    - Type 1: AR inborn error of metabolism – defect in enzyme AGT in liver (normally changes glyoxylate → glycine)
      - ◆ w/o AGT, glyoxylate leaves peroxisome and is converted to oxalate by LDH, XO, and GAO
      - ◆ characterized by nephrocalcinosis, tissue deposition of oxalate (oxalosis) and death from CRF by age 20
        - ◆ increased secretion of oxalic, glycolic, and glyoxalic acids
    - Type 2 (L-glyceric aciduria): deficiency of liver enzyme D-glycerate dehydrogenase and glyoxalate reductase – increase in urinary oxalate
      - ◆ rare, more indolent illness
    - both types have stone formation start in childhood, w/ nephrocalcinosis, interstitial nephritis, and CRF
  - increased hepatic conversion
    - pyridoxine deficiency
    - ethylene glycol ingestion: converted to glycolic acid and glycoaldehyde
    - methoxyflurane anaesthesia
- increased oxalate absorption (enteric hyperoxaluria)
  - malabsorption from any cause increases the colonic permeability of oxalate due to exposure of colon to bile salts

## Chapter 96 Questions - Stones.doc

- loss of Ca in feces, allowing oxalate to exist in soluble form
- tx is unsatisfactory: PO hydration, low-oxalate low-fat diet, Ca carbonate 1-4g PO TID (binds oxalate), cholestyramine 1-4g
- hyperoxaluria in idiopathic calcium oxalate stone disease
  - mild metabolic hyperoxaluria seen in 0.3-50% of stone formers
    - etiology unknown:
      - ◆ altered membrane transport of oxalate: due to increase in oxalate self-exchange across the RBC membrane in 80%
      - ◆ increased dietary protein intake
      - ◆ altered renal excretion of oxalate, increased fractional excretion, increased absorption
  - tx is difficult
    - no-oxalate diet (impossible)
    - pyridoxine: decreases urinary oxalate excretion in 50%
    - thiazides: decrease oxalate excretion and normalize RBC fluxes
    - tyrosine
    - Ca, GAG or fish oil, oxothiazolidine carboxylate

### What is the treatment for primary hyperoxaluria?

- pyridoxine supplements 200-400mg/day
  - acts as a cofactor in conversion of glyoxylate→glycine, lowers oxalate excretion
- increase water intake
- PO citrate, thiazides, P, Mg gluconate
- liver transplant

### Why does hyperuricosuria cause Ca stones?

- uric acid promotes Ca oxalate crystallization by facilitating formation of nuclei
- may nullify effectiveness of naturally occurring inhibitors of Ca oxalate crystal growth

### What are the causes of hyperuricosuria?

- excessive dietary purine
- overproduction of uric acid
  - most pts have normal serum urate levels
- alteration in tubular handling of urate
- 90% male

### What is the tx of hyperuricosuria?

- dietary purine restriction
  - limit red meat, poultry, fish
- allopurinol → s/e: rash, hepatic enzyme abnormalities

### What are the causes of hypocitraturic Ca stones?

- **distal RTA: acidosis most important factor**
- chronic diarrhea: intestinal alkali loss causes metabolic acidosis
- hypomagnesuria
- thiazide-induced hypocitraturia: intracellular acidosis
- enalapril
- idiopathic
  - high animal protein diet
  - exercise
  - high Na intake
  - active UTI
  - intestinal citrate malabsorption

### What are the causes of hypomagnesuria?

- **IBD + malabsorption: most common**
  - tx: Mg oxide and pyridoxine, Mg citrate

### How do sex hormones affect stone formation?

- Ca oxalate stones occur more frequently in men
  - estrogen, progesterone, and T stimulate vitamin D formation

## Chapter 96 Questions - Stones.doc

- T increases renal oxalate deposition and urinary oxalate excretion

### How do nanobacteria affect stone formation?

- nanobacteria are gram -ve cytotoxic atypical bacteria that can produce carbonate apatite
  - internalized by cells, are cytotoxic
  - accumulate in kidney, produce apatite

### What disorders are associated w/ pure Ca P stones?

- more common in women
  - distal RTA
  - primary hyperparathyroidism
  - sarcoid

### Why does type I RTA cause renal stones?

- acidosis in distal RTA causes hypocitraturia
  - causes influx of citrate into renal mitochondria, and inhibits its efflux: reduces citrate excretion in urine
- hypercalciuria
  - due to effects of systemic acidosis on bone demineralization and 2° hyperparathyroidism due to decreased 1,25-D
- increased urinary pH

### How do pts present w/ type I RTA?

- infants: vomiting, diarrhea, FTT, growth retardation
- children: metabolic bone disease and renal stones
- adults: stones (in 70%), nephrocalcinosis
  - 80% of pts are women

### What stones are created in type I RTA?

- Ca phosphate (brushite)
  - oxalate and struvite stones also seen
  - stone formation usually in papillary tips and medulla

### What is the defect in type II RTA?

- defect in proximal bicarbonate reabsorption leading to bicarbonate excretion
- kidney can generate proton gradient and acidify urine
- usually associated w/ Fanconi syndrome
  - increased urinary glucose excretion, amino acids, uric acid, and P
  - don't see nephrocalcinosis and nephrolithiasis

### What is the tx for RTA?

- alkali therapy
  - potassium bicarb or citrate 1-2mmol/kg daily divided in 2-3 doses
- add thiazide if hypercalciuria

### How does one evaluate the pt w/ RTA?

- get lytes and blood gas: r/o hypokalemic, hyperchloremic, non-AG metabolic acidosis
- r/o other causes of acidosis by hx/px
- urine pH: if > 5.5, dx is type I RTA
  - if absent acidosis w/ urine pH > 5.5, perform ammonium chloride loading test and measure urine bicarb
  - if urine pH does not decrease to < 5.5, dx is incomplete distal RTA
- if bicarbonaturia present, perform bicarb loading test
  - if fractional excretion of bicarb is > 15% at normal serum levels, dx is type II RTA
- if hyperkalemia present, dx is type IV RTA

### How do sex hormones affect renal stones?

- Ca oxalate stones are more common in men
  - testosterone increases renal oxalate deposition and urinary oxalate excretion
  - estrogens decrease urinary oxalate excretion

### In which clinical situations is an evaluation for RTA indicated?

- calcium P stones

## Chapter 96 Questions - Stones.doc

- recurrent stones > 2/yr
- bilateral stones
- medullary nephrocalcinosis
- MSK
- hypocitraturia
- hypokalemia
- chronic pyelo
- azotemia

### What factors control uric acid crystallization?

- **supersaturation of urine w/ uric acid**
  - overproduction of uric acid
- prolonged acidity in urine
  - less soluble in acid urine
- presence of gout
  - excrete less ammonium and more acid
- low urine volume

### What ethnic populations have increased uric acid stones?

- Jewish, Italian

### What are the causes of uric acid stones?

- Primary
  - increased uric acid intake
- Secondary
  - gout
  - Lesch-Nyhan
  - myeloproliferative d/o: ALL
  - chemo: cell necrosis, releasing uric acid

### What is the frequency of uric acid stones in gout?

- 20%

### What genetic disorder is associated w/ high levels of serum uric acid?

- Lesch-Nyhan syndrome
  - deficiency/lack of hypoxanthine-guanine phosphoribosyl transferase (HGPT)
  - X-linked recessive d/o
  - characterized by self-mutilating behaviors such as lip and finger biting and/or head banging → dental extraction to prevent

### What is the management for uric acid stones?

- observe daily urine pH
- r/o neoplastic disease
- hydration, alkali, allopurinol, diet (HAAD a uric acid stone)
  - drink 1.5-2L per day
  - alkalinize urine to 6.5-7: Na bicarb 650mg q6-8h → s/e: flatulence
  - allopurinol 300-600mg/d if hyperuricemia or if uric acid excretion > 1.2g/d

### What is required to form struvite stones?

- urine pH > 7.2
- ammonia in urine
- infection in urine w/ urease producing bacteria → creates ammonia

### How do urease producing bacteria cause stones?

- hydrolyze urea to CO<sub>2</sub> and NH<sub>3</sub>
- NH<sub>3</sub> takes up H<sup>+</sup> to form NH<sub>4</sub><sup>+</sup>
- CO<sub>2</sub> hydrated to carbonic acid (H<sub>2</sub>CO<sub>3</sub>), which releases 2H<sup>+</sup> and CO<sub>3</sub><sup>-</sup> → increases pH

### What organisms can produce urease?

- Gram -ve

## Chapter 96 Questions - Stones.doc

- *Proteus mirabilis*: most common
- *Hemophilus*
- *Bacteroides*
- Gram +ve
  - *Staphylococcus*
  - *Corynebacterium*
- Mycoplasma
  - *Ureaplasma urealyticum*
- Yeasts
- *E.Coli* does not produce urease

### What is the clinical presentation of struvite stones?

- malaise, weakness, loss of appetite
- can form staghorns
- fever, loin pain, dysuria, LUTS, hematuria
- XGP
- hypercalciuria

### What are the RF for struvite stones?

- more common in women
- foreign body in GU tract
- neurogenic bladder
- indwelling catheter
- urinary diversion
- lower tract voiding dysfunction

### What is the treatment for struvite stones?

- initial tx: remove stones completely (PCNL), followed by supportive medical therapy
  - antibiotics: cipro
  - meds: acetohydroxamic acid → irreversible inhibitor of urease
    - significant s/e: use w/ medical tx if surgery contraindicated
  - diet: low-Ca, low-phosphorus w/ aluminum gels
    - aluminum binds P, decreasing urinary phosphate
  - irrigation and chemolysis: Suby G solution
    - no irrigation until urine completely sterile
    - can use through NT in pts that cannot undergo surgery
    - irrigate 1<sup>st</sup> w/ NS at 120cc/hr x 24-48h, then w/ solution

### What is the role for anatomic nephrolithotomy?

- infundibular stenosis
- distorted intrarenal anatomy

### What are the s/e of acetohydroxamic acid?

- DVT, tremor, h/a, palpitation, edema, N/V, loss of taste, hallucinations, rash, diarrhea, alopecia, abdo pain, anemia

### What is the cause of cystinuria?

- cystine stones 1% of all stones
- AR disorder of transmembrane cystine transport in intestine and kidney → only homozygotes form stones
- codes for an abnormal transport system involving cystine, ornithine, lysine, arginine (COLA)
  - ornithine, lysine, and arginine freely soluble → do not form stones
- secretion and paracellular leakage of cystine are normal, but impaired reabsorption across brush border in kidney
  - decreased cystine absorption in intestine
  - decreased cystine resorption in PCT
- cystine poorly soluble in normal urine pH

### What is the management of cystinuria?

- inspect 1<sup>st</sup> morning urine for hexagonal crystals of cystine
  - cyanide-nitroprusside colorimetric test
  - quantification of urinary cystine excretion by amino acid chromatography
- surgical treatment for stones



## Chapter 96 Questions - Stones.doc

- diet: low-methionine → decrease meat, poultry, fish, dairy  
→ poor compliance due to unpalatability
- hydration: fruit juices → gives both water and alkali
- alkalization of urine above 7.5  
→ **Na bicarb** 15-25g/d and K citrate 15-20mmol BID-TID  
→ **glutamine** 2g/day in divided doses → reduces urinary cystine excretion  
→ K-citrate
- **acetazolamide** 250mg PO TID: increases urinary bicarb excretion by inhibiting carbonic anhydrase
- **D-penicillamine**: bind cystine, form soluble complex  
→ +++ s/e: GI (N/V/D), impaired taste/smell, dermatologic complications, hypersensitivity, F/C, arthralgia
- **alpha-mercaptopyrroline glycine**: binds cystine
- capoten
- percutaneous chemolysis: N-acetylcystine, tromethamine, sodium bicarb, D-penicillamine

### What is the appearance of cystine crystal on UA?

- hexagonal

### Which stones are radiolucent on Xray?

- pure uric acid
- dihydroxyadenine
- xanthine
- indinavir
- triamterene
- matrix
- silicate stones
- ephedrine or guaifenesin

### What is the enzyme deficiency in dihydroxyadenine stones?

- lack of enzyme adenine phosphoribosyl transferase  
→ interferes in normal pathway of dietary adenine  
→ adenine then oxidized to 8-OHadenine and 2,8-diOHadenine (insoluble, precipitates)
- radiolucent, resemble uric acid stones
- alkalization may promote stone growth  
→ dx by assay of adenine phosphoribosyl transferase activity in RBC

### What is the etiology of xanthine stones?

- IEM inherited as AR trait  
→ deficiency of xanthine oxidase: blocks conversion of hypoxanthine → xanthine → uric acid
- pts given allopurinol for gout may make xanthine stones
- may also occur in pts w/ Lesch-Nyhan syndrome that are treated w/ large doses of allopurinol  
→ deficiency of hypoxanthine guanine phosphoribosyltransferase
- tx: increased water intake

### What is the cause of silicate stones?

- pts taking large amount of antacids w/ silicates: Mg

### What is the etiology of matrix stones?

- UTI w/ urease-producing organisms

### What are the causes of ammonium acid urate calculi?

- ureolytic infection in presence of excessive uric acid excretion
- urinary phosphate deficiency
- low fluid intake in children of developing countries
- **laxative abuse**

### What OTC meds can cause stones?

- ephedrine or guaifenesin

### Which stones are radiolucent on CT?

- indinavir

## Chapter 96 Questions - Stones.doc

- some matrix stones

### Describe the clinical presentation of the pt w/ a stone.

- Hx
  - renal or ureteral colic: abrupt, affects pt w/ at rest → usually in night or early morning
  - writhing in pain: worse if stone moving
  - radiation to lateral flank and abdomen, to area of groin and testicle
  - LUTS if near bladder
  - N/V/D
- Px
  - fever: if infected
  - tender to palpation
- UA
  - hematuria in 85%
  - pyuria
  - crystals

### Why do pts w/ stones get N/V/D?

- N/V: autonomic NS transmits pain, and celiac ganglion serves kidneys and stomach
- D: due to local irritation

### What are the 5 locations where a stone can become impacted?

- UPJ
- UVJ: most common
- pelvic brim, where ureter crosses iliac vessels
- calyx in kidney
- posterior pelvis, where ureter crossed anteriorly by pelvic vessels and broad ligament

### What is the appearance of each type of urinary crystal on R&M?

- Calcium oxalate monohydrate: dumbbell/hourglass
- Calcium oxalate dihydrate: envelope/pyramid
- Calcium phosphate-apatite: amorphous
- Calcium hydrogen phosphate dihydrate (brushite): needle shaped
- **Cystine: hexagon**
- Struvite (MAP): coffin lid
- Uric acid: amorphous

### How large must stones be to be seen on KUB?

- Ca stones: 2mm
- cystine: 3-4mm

### What are the signs of ureteric stone on CT?

- hydroureter
- unilateral stranding
- hydronephrosis
- nephromegaly
- edematous ureteric wall

### What are the indications for bypassing a stone?

- significant obstruction
  - stones > 6mm unlikely to pass, may admit to expedite therapy
- renal deterioration
- pyelo/obstructing stone w/ infected urine or fever
- unremitting pain
- solitary kidney

### What are the effect of ureteral obstruction on renal function?

- rapid redistribution of RBF from medullary to cortical nephrons
- decrease in GFR and RPF
- 3 phases of renal response to obstruction

## Chapter 96 Questions - Stones.doc

- 0-5h: ureteral pressure and RPF increase
- 5-12h: RBF falls and ureteral pressure rises
- 12-18h: RBF and ureteral pressure fall
- hypertrophy of ureteral musculature → scarring
- UTI totally impairs ureteral function
- irreversible renal functional loss within 5-14d
  - slight recovery only by 4mo
  - can give pts 4 weeks to pass stones spontaneously

### What are the forms of stone analysis available?

- chemical analysis: abandoned → not accurate
- thermal analysis
- optical methods
  - optical crystallography and x-ray crystallography
  - IR spectroscopic analysis
  - polarizing microscopy
  - near IR reflectance analysis
  - thin section TEM analysis

### Who is at high risk of getting stones?

- FHx stones
- bone/GI disease
- gout
- chronic UTI
- nephrocalcinosis
- other medical RF
- multiple stones initially
- recurrence within 1 year
- **children w/ stone**
  - all these pts should have more complete metabolic evaluation and specific medical therapy

### What is the medical evaluation of a stone?

- Hx
  - age, sex
  - diet and fluids: milk, vitamins
  - medications
    - steroids: increase enteric absorption of Ca
    - antacids, diuretics, vitamin D: cause hypercalciuria
    - chemo: lead to cell breakdown, can cause uric acid stones
    - Dyazide: contains triamterene
    - vitamin A, D
    - enalapril
  - infection: urease producing bacteria
  - activity level: immobilization → bone demineralization
  - systemic disease: primary hyperPTH, RTA, gout, sarcoid, granulomatous diseases, GI (IBD, bowel OR), hypercalcemia, malignancy, hyperthyroid
  - genetics: FHx stones
  - anatomy: MSK
  - previous surgery: bowel resection, chronic diarrhea
  - occupation
  - stress: lower family income, mortgage problems, emotional life events associated w/ stone disease
- First stone
  - IVP, UA, urine C&S, CBC, LFT, lytes, BUN, Cr, Ca profile, send stone
- Recurrent/multiple stones or high risk (FHx, bone/GI disease, gout, chronic UTI, nephrocalcinosis)
  - 24h urine in addition: at least 1 set
- Imaging
- repeated assessment better than single

### What is the recurrence rate for stones?

- 7% per year

## Chapter 96 Questions - Stones.doc

→ 50% in 10 years

### How does dietary protein form stones?

- proteins increase urinary Ca, oxalate, and uric acid excretion
- increases endogenous acid production and secretion
- acidosis inhibits Ca resorption in distal nephron, increasing urinary Ca excretion
- metabolism of MET results in sulfate formation, causing hypercalciuria
- acidosis decreases urinary citrate excretion
- increase in dietary protein or purine causes increased uric acid excretion
- obesity causes impaired CHO tolerance and inappropriate Ca response to glucose ingestion

### How does dietary sodium cause stones?

- increased Na intake causes natriuresis
- Na and Ca resorbed at common sites along distal tubule
- natriuresis causes hypercalciuria

### What is the medical treatment of a stone?

- General
  - hydration
    - distilled water, tap water w/ citrate
      - ◆ failure to increase urine output is most important cause of stone recurrence
    - risk of stone formation decreased 60% in RNs drinking 1 glass wine daily
  - diet
    - limit meat intake to 8oz daily
      - ◆ protein increases urinary calcium, oxalate, and uric acid excretion (even in normal pts)
    - increase citrus intake
    - increase fiber: whole wheat bread, cereals
    - reduce weight
      - ◆ obesity associated w/ impaired CHO tolerance and inappropriate Ca response to glucose ingestion
        - ◆ may be a cause of hypercalciuria
    - **normal Ca intake:** do not overindulge
      - ◆ if restrict, less available to bind oxalate, possibility of -ve Ca balance, osteoporosis
      - ◆ Ca supplements do not reduce risk further
    - **decrease Na intake:** natriuresis promotes hypercalciuria
    - avoid oxalate/phosphate containing foods: oxalate-free diet is difficult
- Specific → no evidence that it is more efficacious
  - HCTZ: for Ca oxalate stones 50mg PO BID
    - stimulate Ca resorption at DCT and increase excretion of Na
    - stimulate PTH in renal resorption of Ca
    - may increase urinary excretion of Mg and Zn
    - s/e: lassitude and sleepiness, decreased libido, **hypoK**, lipid, glucose intolerance, hyperuricemia
      - ◆ may need to start on K supplementation
  - orthophosphates: for Ca oxalate stones
    - decrease production of vitamin D w/o affecting PTH, increasing citrate and pyrophosphate
    - decreases calcium in urine by 50% in pts w/ absorptive hypercalciuria, by 25% in pts w/o this d/o
      - ◆ used less frequently now: no evidence, s/e
    - **increases P excretion → contraindicated in struvite stones**
    - s/e: GI disturbances, diarrhea
  - sodium cellulose phosphate 10-15g/day in divided doses
    - nonabsorbable resin: binds Ca in gut, and inhibits intestinal Ca absorption
    - binds Ca in gut, and increases urinary oxalate excretion and absorption → may increase oxalate in urine
      - ◆ **restrict oxalate in pts on this drug**
    - poorly tolerated: N/V/D, may cause -ve Ca balance and PTH stimulation
    - binds Mg, causing hypomagnesuria → **start pts on Mg oxide simultaneously**
    - used for documented cases of absorptive hypercalciuria only
  - allopurinol: for uric acid stones 100mg PO TID
  - citrates: for Ca oxalate stones 30-60mEq/d divided doses → efficacy uncertain
    - potassium citrate, sodium potassium citrate: no prospective RCT has shown superiority of one over the other
  - magnesium: w/ sodium cellulose phosphate for absorptive hypercalciuria type 1, or w/ K citrate in pts w/ chronic diarrhea

## Chapter 96 Questions - Stones.doc

- Mg oxide or Mg hydroxide
  - ◆ both poorly absorbed
- decreases renal tubular citrate resorption through the chelation of citrate → increases urinary excretion of citrate
- s/e: GI intolerance

### How can one use selective therapy in the prevention of kidney stones?

- low urine volume: increase fluid intake
- absorptive hypercalciuria
  - type I: sodium cellulose phosphate, thiazides
  - type II: low-Ca diet, sodium cellulose phosphate
  - type III: orthophosphates
- hypocitraturia: K citrate, sodium K citrate
- hypomagnesuria: Mg citrate
- hyperuricosuria: allopurinol
- uric acid stones: allopurinol, K salts
- enteric hyperoxaluria: pyridoxine 200-400mg PO TID, PO citrate, thiazides, P, Mg gluconate
- chronic diarrhea: cholestyramine, K salts
- infection stones: acetohydroxamic acid
- cystinuria: alpha-MPG, D-penicillamine

### What is the most common composition of bladder stones?

- infected: struvite
- non-infected: uric acid

### What are the causes of bladder stones?

- urinary retention
  - stricture
  - BPH
  - bladder diverticulum
  - neurogenic bladder

### What are the sx of bladder stones?

- LUTS, intermittent painful voiding, terminal hematuria, SP pain, stranguria
- interrupted voiding stream
- children: priapism, nocturnal enuresis

### How can one prevent bladder stones?

- eliminate obstruction
- correct stasis of urine
- remove foreign body
- irrigation w/ 0.25% or 0.5% acetic acid solution to prevent struvite stones if catheter left for long period

### How does one form prostatic stones?

- inorganic salts impregnate corpora amylacea, converting them into stones
- infection also contributes
- ochronosis

### What is the composition of prostate stones?

- Ca phosphate

### What are the potential causes of prostatic calcification?

- radiation, TURP, cryotherapy, prostatic stents

### What is the treatment of prostatic calculi?

- asymptomatic: no treatment indicated
- symptoms: TURP or SP prostatectomy
  - RP if multiple stones and intractable UTI

### What are the reasons women don't get urethral stones?

- short urethra

## Chapter 96 Questions - Stones.doc

- infrequency of bladder stones in women

### How can one classify preputial stones?

- calculi arising from inspissated smegma
- calculi that form in stagnant urine
- calculi expelled from urethra/bladder into preputial sac through meatus or by ulceration through fossa navicularis

### What are the causes of stones in children?

- non-urologic causes
  - low-birth weight: < 1500g
    - 30-90% of very LBW kids tx w/ Lasix have stones
    - can occur in kids that have not received furosemide
  - Lasix
  - dietary Na, Ca, vit D supplementation
  - steroids
  - theophylline
  - metabolic or resp acidosis → hypocitraturia
  - TPN → increases oxalate excretion in LBW babies
- urologic causes
  - **UPJO: most common anatomic lesion causing stones**
  - meningomyelocele, neurogenic bladder

### What is the presentation of a stone in children?

- M:F 2:1
- rare in blacks
- infected stones more common in kids < 4 yrs
- rarely present w/ colic (only 15%)
  - 70% present w/ UTI
  - hematuria, abdo pain
- average age 8-10
- hypercalcemia is most common abnormality seen (if non-infected, non-UPJO)
- higher incidence of recurrence in kids

### What is the treatment of the child w/ a stone?

- 2/3 pts require procedure to remove the stone → much higher than adult population

### What regions have high incidences of bladder stones?

- North Africa, Middle East, Burma, Thailand, Indonesia
  - traced to common practice of feeding infants human breast milk and cereal foods (polished rice or mullet)
    - milk and cereals low in phosphorus
    - causes high peaks of urinary ammonium excretion
  - high ingestion of oxalate containing vegetables

### How does pregnancy affect renal stone disease?

- multiparous women more predisposed than primiparous women
- absorptive hypercalciuria and hyperuricosuria present
  - due to increased vitamin D manufactured in placenta, w/ PTH suppression
- increased quantities of inhibitors and increased urine output
- pregnancy masks signs of renal colic
  - present w/ abdo pain, fever, bacteriuria, microhematuria
- dx w/ KUB and US
  - KUB = 20 mrad (toxic dose to fetus is 25-80 rad) → < 1% of toxic dose
  - avoid fluoro
  - modified IVP has minimal risk: scout, 30sec film, 20 min film
- 66-85% pass stone when treated conservatively
  - hydration, analgesic, antibiotics if needed
- stent placement preferably done in late 2<sup>nd</sup> or 3<sup>rd</sup> trimester only, change q2mo
  - use minimal radiographic or US monitoring
  - perc NT if needed
- very risky to perform ureteroscopy/basketing

### **Chapter 96 Questions - Stones.doc**

- anaesthesia-related premature labour, spontaneous abortion, and IUGR
- **pregnancy is an absolute contraindication to ESWL**







**Chapter 97**

**• Ureteroscopy and Retrograde Ureteral Access •**

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**What are the indications for ureteroscopy?**

- Diagnostic
  - filling defect on IVP/CT/MR
  - hematuria from upper tract
  - unilateral +ve cytology
  - surveillance of pts w/ previous upper tract ca
- Therapeutic
  - stones
  - strictures
  - low-grade/stage TCC
  - FB removal

**What are the indications for ureteral stent?**

- assisting passage of wire into UO
- passive dilation of ureter pre-intervention
- draining upper tract after ureteroscopy/stone manip
- bypassing obstruction
- post-op support

**What are the indications for balloon dilation?**

- UO and intramural ureter before ureteroscopy
- ureteral stricture
- infundibular stenosis
- mouth of calyceal diverticulum
- perc tract for antegrade renal/ureteral access
- SP tube tract during endoscopic eval of bladder

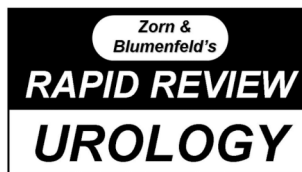
**What maneuver is performed to evaluate the upper tract in hematuria?**

- rigid ureteroscope passed **without guide wire**

**What are the complications of ureteral access and ureteroscopy?**

- ureteral perforation
- ureteral stricture
- ureteral avulsion
- bleeding
- sepsis
- balloon rupture
- laser cutting guidewire





## **Chapter 98**

### **• Percutaneous Approaches to the Upper Urinary Tract •**

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#### **What can be done to minimize the radiation exposure during fluoroscopy?**

- fluoro beam under table → extra layer of shielding
- lead apron and thyroid shield
- minimize fluoro time
- collimate → narrows the beam and limits the imaging area to exact position of interest
- radiation detection devices (dosimeters)
- lead glasses and gloves

#### **What is the total radiation effective dose equivalent limit for occupational exposure?**

- 5 rem

#### **What is the major source of the radiation dose received by the endourologist?**

- scattered radiation from the patient

#### **Where is the posterior segmental renal artery in relation to posterior renal surface?**

- located in the middle or upper ½ of posterior renal surface  
→ may be punctured if excessively medial needle puncture

#### **What is Brodel's line?**

- avascular plane b/w anterior and posterior blood supplies

#### **Describe the technique of percutaneous nephrostomy.**

- cysto: open-ended 6F ureteral catheter +/- occlusion balloon passed, secured to a Foley  
→ nephrostogram: can use air → lighter than urine, will identify posterior calyces 1<sup>st</sup> w/ pt prone  
➤ will not interfere w/ evaluation of residual stones due to retained/extrav contrast
- pt prone  
→ bolsters, pad knees, ankles, feet
- endourology drape w/ plastic side pouch for irrigant fluids
- choose tract  
→ posterior calyx, as major vascular structures are avoided  
→ look w/ C-arm at 90 degrees, then 30 degrees away and towards  
→ overlying skin site marked w/ snap
- 18G angio needle advanced in plane of fluoro beam w/ C-arm 30 degrees toward surgeon  
→ look for "bull's eye sign"  
→ advance in 1-2mm increments  
→ depth monitored by rotating back to vertical position  
→ can place middle calyx Amplatz sheath, and rotate kidney down to place 2<sup>nd</sup> needle in upper calyx
- if seems to be in a calyx, remove stylet, look for urine  
→ advance stiff guide wire across UPJ  
→ dilate to 30F  
➤ serial dilators to 10F, then balloon dilated to 30F (20atm)

#### **Why should one not puncture the renal pelvis directly?**

- risk of injuring posterior branch of renal artery
- tract created from puncture provides no stability for nephrostomy tube: lacks parenchymal support

#### **What are the possible ways to gain perc access?**

- fluoroscopic anterograde approach  
→ bull's eye sign  
→ triangulation

## Chapter 98 Questions - PCNL.doc

- blind puncture: if obstruction of lumen and pelvis cannot be opacified
- fluoroscopic retrograde approach: wire passed through ureteral catheter out selected calyx
  - may be useful in cases of hypermobile malrotated or malpositioned kidneys
  - Lawson system
    - wire passed into upper tract, 7.5F Torcon deflectable catheter placed over, and wire removed
    - catheter advanced into posterior calyx under fluoro
    - wire pushed through kidney under fluoro through catheter
    - tract dilated to 10F
  - Hunter-Hawkins system
    - similar to Lawson, but many catheters and guide wires help gain access
    - 0.018 "rocket" wire penetrates scar
- US approach
- CT/MRI approach

### What are the options for dilation of the tract?

- fascial dilators: tips can perforate renal pelvis medially
  - main advantage: safety → once 8F catheter in place, dilation unlikely to kink wire, low incidence of perf
  - use in pts w/ previous retroperitoneal surgery, inflammation, or previous percs
  - main drawback: integrity of wire
- Amplatz dilators (blue polyurethane)
  - dilate over 8F polytef catheter that sits over a wire
  - distal end of catheters should not be passed down beyond UPJ
- **Alken** metal coaxial dilators
  - for pts w/ previous surgery and associated fibrous tissue
  - difficult to control pressure during dilation
- balloon catheters
  - more expensive, ? less hemorrhage
- **dilation of the tract must be performed under fluoro**

### Describe the technique of triangulation.

- C arm placed over pt in vertical position
- retrograde performed
- skin over desired calyx marked = medial extent of needle penetration
- C arm rotated 30 degrees toward MD for end on view of calyx, skin site marked
- move in vertical line inferiorly to 1-2cm below 12<sup>th</sup> rib = site of needle entry
- needle advanced to junction of vertical plane and 30 degree plane

### What types of nephrostomy tube drainage are available?

- pigtail
- Cope loop: difficult to remove if encrusted
- Malecot
- Foley
- reentry tubes
  - can access the renal pelvis and ureter, has wide lumen, soft material, and safety in removing tube
  - main disadvantage: tip of catheter sits in ureter
- circle loop nephrostomy
  - easily changed, rarely causes UTI, and can be used for irrigation
  - good for pts that need long-term upper tract diversion: fewer tube changes

### What are the complications of percutaneous access to the kidney and their treatments?

- complication rate 8.7% for direct upper pole calyx puncture
- vascular injury: 1-3% risk of serious vascular injury
  - transfusion rate: 3-23%
    - large complex stones: 11%
    - increases w/ more punctures
  - blood loss: 0.8% angio/embolization need
    - during dilation
    - after procedure
  - AV fistula
  - pseudoaneurysm

## Chapter 98 Questions - PCNL.doc

- laceration
- lung injury
  - pneumothorax: 0-4%
  - pleural effusion: 0-8%
  - hemothorax → drain w/ NT in chest → 32F chest tube → thoracoscopy
- renal pelvis injury → use nephrostomy/ureteral drainage until sealed
- bowel perforation (< 1%) → separate w/ ureteric stent + catheter in colon
  - consider getting CT preop if enlarged colon
- splenic/liver injury → conservative tx after recognition
- sepsis → abx
- fluid overload and hyponatremia → Lasix and mannitol
  - fluid extravasation: large amounts absorbed: always use NS to prevent hyponatremia
- technical
  - loss of NT → replace
  - extravasation of contrast
  - access
    - cannot access collecting system → refer
    - guide wire kinks → repeat NT
    - hypermobile kidney → fix w/ 1<sup>st</sup> puncture, perform 2<sup>nd</sup>

**What % of pts undergoing perc puncture of kidney require angio and embolization for bleeding?**

- 0.8%

**What can be done to treat blood loss during perc?**

- working sheath used to tamponade
- inflate Councill balloon catheter adjacent to injured venous segment
- high pressure Kaye tamponade balloon: keep for 2-4 days
  - urine drainage through inner lumen of catheter
  - remove under fluoro: allows for immediate reinsertion if more bleeding
- angio and embolization
- transfusion
- open surgical exploration

**What is the rate of lung injury during perc?**

- increased if supra-11
- supra-12
  - pneumothorax 4%
  - pleural effusion 8%

**How does one diagnose colon perforation during perc?**

- **rare: 0.6% retrorenal colon**
- intraoperative hematochezia
- peritonitis
- sepsis
- gas/feces drainage from NT
- contrast seen in colon during post-op nephrostogram

**How is a bowel perforation treated?**

- extraperitoneal colon perforation
  - treat conservatively
    - ureteral stent
    - NT withdrawn to lie w/i lumen of colon
    - broad spectrum antibiotics
    - colostogram in 7-10d
    - remove tube if no communication
  - surgical correction only if sepsis/peritonitis, intraperitoneal perforation
- duodenal perforation
  - place NT
  - NG tube
  - TPN

## Chapter 98 Questions - PCNL.doc

### What are the causes of ureteral obstruction?

- Intramural: scarring, dysplastic muscle
- Intraluminal: tumour, stone, clot, inflammatory mass, fungal bezoar
- Extrinsic: lower pole anterior crossing vessel, RPF, retroperitoneal lymphadenopathy

### How does perc access differ in an infected vs. uninfected system?

- emergency access needed in the acute case
- aspirate infected material, introduce only slight amount of contrast to prevent pyelovenous backflow
- no attempt made to obtain antegrade nephrostogram in infected system
- infracostal puncture to prevent transpleural passage, even if in upper pole
- stone therapy only 5-7d later after antibiotics

### What are the cyst related problems in ADPKD?

- flank pain: 30%
- pyelo: 30%
- stones: 34%
- htn: 21%
- perinephric abscess: 8%
- mass: 15%
- hematuria: 19%
- renal failure: 17%
- only 8% of cysts become symptomatic in normal pplx

### What materials can be used to sclerose renal cysts?

- 95% EtOH: 25% of cyst volume x 10-20min
- bismuth phosphate: 5-10ml
- tetracycline
- Na morrhuate
- polidocanol 3%
- povidone-iodine

### Where should the perc tract be placed for drainage of a renal abscess?

- infracostal, even if in upper pole
- prevents pleurotomy and empyema

### What is the success rate of perc drainage of renal abscess?

- 82%

### What are the most common predisposing factors for the formation of renal abscesses?

- renal stones
- renal obstruction
- DM
- multisystem disease
- recurrent pyelo

### What is the key factor that determines if the outcome of the perc approach to renal abscesses is successful?

- whether abscess is simple or loculated
- simple: 80% success
- loculated: 45% success

### What are the causes of urinoma?

- renal trauma: most common
- ureteral obstruction w/ forniceal rupture
- iatrogenic perf of collecting system
- r/o pancreatic pseudocyst if collection is L-sided

### What 3 factors are required for urinoma to form?

- ureteral obstruction
- extravasation from the collecting system

## Chapter 98 Questions - PCNL.doc

- functioning kidney

### What consists of the workup for a urinoma?

- IVP
- CT
- retrograde

### What is the treatment of a urinoma?

- place perc drain: send fluid for Cr and amylase
- if ureteral obstruction present, or drains x days, place stent or NT to divert urine
- biopsy fistula tract to r/o malignancy
- surgical exploration and formal closure

### What are the most common organisms causing perinephric abscess?

- *E.Coli* or *Proteus*

### Why is necessary to perform puncture of perinephric abscess below the 12<sup>th</sup> rib?

- prevent inadvertent pleurotomy → empyema

### What are the contraindications for percutaneous drainage of perinephric abscess?

- uncorrected coagulopathy
- suspicion of hydatid fluid collection

### What is the mortality rate of perinephric abscess?

- untreated: > 80%
- treated: 8-22%

### What are unfavourable factors for a perc approach to a perinephric abscess?

- fungal infection
- calcification of mass wall
- calcified debris w/i the mass
- thick purulent drainage
- multiloculated cavity
- markedly diseased nonfunctioning kidney (indication for nephrectomy)
- infected hematoma

### What are the sx of lymphocele?

- usually due to compression of adjacent structures
  - flank pain from hydro
  - ipsi lower extremity edema
  - constipation
  - decreased bladder volume
  - abdominal mass

### What are the fluid characteristics of a lymphocele?

- Cr and lytes reflect serum values
- cholesterol and protein lower than serum
  - if upper retroperitoneum, chylous fluid collects: cloudy, high triglycerides and proteins
- lymphocytes present

### What options are available for treatment of a lymphocele?

- simple aspiration
  - sufficient for collections < 150cc
  - if larger, <20% success
- perc drain x days-weeks
- sclerotherapy w/ EtOH or tetracycline: overall success rate 70-80%
- flexible ureteroscopic access and fulgurization
- open surgical drainage
- laparoscopic drainage and marsupialization

## **Chapter 98 Questions - PCNL.doc**

### **What are the causes of a retroperitoneal hematoma?**

- blunt renal trauma
- penetrating renal trauma
- anticoagulation
- vascular lesion
- tumour
- surgical complication: perc, ESWL, renal bx

### **What is the natural hx of retroperitoneal hematoma?**

- slow spontaneous resolution

### **What are the indications for intervention for retroperitoneal hematoma?**

- hematoma extremely large  
→ compromising respiratory function
- expanding
- impairing renal function
- hypotension
- spontaneous renal hemorrhage in pts w/ no hx anticoagulation, vasculitis or trauma  
→ consider nephrectomy: 50-70% chance of **RCC**

### **What are the sources of false negative test results for a Whitaker?**

- extravasation during test
- failure to fill renal pelvis completely before reading pressure

### **How does one perform a Whitaker test?**

- place NT and urethral catheter
- infuse dilute contrast into collecting system at **10cc/min**
- read pressure in renal pelvis and bladder q5min until steady pressure in both areas
- if difference in pressure < 13-15cmH<sub>2</sub>O, non-obstructed
- if > 22cmH<sub>2</sub>O, indicates obstruction
- equivocal if b/w 15 and 22

### **What is the nephrectomy rate from renal biopsy?**

- nephrectomy rate 0.06%
- mortality rate 0.08%
- minor complication 5%
- **bleeding requiring transfusion 1-5%**
- open surgical tx of complication 0.3%
- infection, fistula 0.1%

### **What is the success rate of renal biopsy?**

- provides adequate tissue for diagnosis in >90% pts

### **What are the options for percutaneous ablation of renal cysts?**

- direct approach (transcystic)
  - retrograde catheter placed, indigo carmine + contrast nephrostogram
  - cyst percutaneously punctured: should be clear → if blue, collecting system entered, need to pass again
  - safety and guide wire coiled in cyst, tract dilated
  - cyst wall punctured into collecting system and widely opened
  - remaining cyst wall fulgurated, transcystic NT placed
  - NT removed when nephrostogram shows obliteration of cavity: days to weeks
- direct approach (transparenchymal)
  - cyst punctured through parenchyma, collecting system not entered
  - cyst wall abutting retroperitoneum resected, tube placed into cyst
- indirect approach
  - collecting system percutaneously entered away from cyst
  - cyst percutaneously filled, cyst sharply entered from collecting system
  - far wall fulgurated, NT placed

### **What approach should always be used for percutaneous removal of a fungal bezoar?**



## Chapter 98 Questions - PCNL.doc

- subcostal approach  
→ traversal of pleural may result in fungal empyema

### What pts are at risk of developing fungal bezoar?

- DM
- antibiotics
- catheters
- immunosuppressed
- renal tx pts

### What is the tx of a fungal bezoar?

- amphotericin B or 5-FC
- topical irrigation of affected collecting system w/ amphotericin B (50cc/L at 25-50cc/hr)
- percutaneous removal of bezoar

### Describe the technique for percutaneous removal of a fungal bezoar.

- retrograde catheter placed  
→ renal pelvis irrigated w/ amphotericin B
- infracostal percutaneous nephrostomy  
→ never do supracostal → risk of fungal empyema
- suction from ultrasonic lithotripter used to remove
- flexible nephroscope to ensure all fragments removed
- 22F Councill tip catheter
- nephrostogram POD1  
→ if no fragments, irrigate w/ amphotericin B  
→ remove POD 3-4

### What is a calyceal diverticulum?

- congenital diverticulum arising from fornix of minor calyx
- lined w/ transitional epithelium

### Describe the technique for percutaneous ablation of a calyceal diverticulum.

- cystoscopic placement of ureteral catheter + occlusion balloon
- nephrostogram completed
- fluoroscopically guided puncture into diverticulum
- guide wire coiled in diverticulum → 2<sup>nd</sup> can be placed if large
- tract into tic is dilated w/ balloon
- sheath introduced into diverticulum, then nephroscope: stones removed if present
- indigo carmine introduced through ureteral catheter to identify neck
- wire passed through neck into renal pelvis
- entire surface of diverticulum fulgurated except for area surrounding neck
- dilate neck w/ balloon or cut under direct vision
- place NT across diverticulum into renal pelvis

### What are the options for treating calyceal diverticulum?

- direct percutaneous approach: works in 80-90%
- **indirect percutaneous approach → mentioned only to be condemned; not successful**
- ureteroscopic approach
- ESWL: 70% asymptomatic, but 80% still have stones in tic after tx

### What is the usual cause of infundibular stenosis and hydrocalyx?

- usually associated w/ inflammation, **renal TB**, obstructive stone, or prior renal surgery

### What is Fraley's syndrome?

- infundibular stenosis caused by an upper pole-crossing segmental renal artery

### What are the various ways of dealing with a stenotic infundibular tract?

- balloon dilation: 60% success
- cut under endoscopic control: 67-80% success → **less successful than calyceal diverticulum**

**Chapter 98 Questions - PCNL.doc**

- incision should be made along less vascular superior and inferior aspects of middle calyceal infundibulum or medial and lateral aspects of the upper calyceal diverticulum
- avoid single deep cut: get ++ bleeding



## Chapter 99

### • **Surgical Management of Urinary Lithiasis** •

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#### **Where is Brodel's line?**

- 5mm posterior to convex border of kidney

#### **What factors are associated w/ poor results of ESWL?**

- large renal calculi
- stones w/i dependent or obstructed portions of the collecting system
- composition: Ca oxalate monohydrate and brushite
- obesity
- body habitus that inhibits imaging
- unsatisfactory targeting of stone

#### **What factors affect the management of renal stones?**

- Stone factors
  - size
  - number
  - composition
- Renal anatomy
  - obstruction/stasis
  - hydro
  - UPJO
  - calyceal diverticulum
  - horseshoe / other ectopic/fusion anomalies
  - lower pole
- Patient factors
  - infection
  - obesity
  - body habitus deformity
  - coagulopathy
  - age: juvenile, elderly
  - hypertension
  - renal failure
  - pregnancy

#### **What is the natural hx of renal calculi?**

- 50% of pts get sx
  - 50% of these need tx
- 50% increase in size

#### **What are the indications for treatment of an asymptomatic calyceal stone?**

- pediatric patient
- solitary kidney
- high risk profession (pilots)
- women considering pregnancy

#### **What is the most important factor in determining treatment of a stone?**

- stone burden (size and number)

#### **What is the approach to treatment of a stone according to stone size?**

- stones < 10mm: 50-60% of all stones
  - ESWL first-line, regardless of composition or location: stone-free rate 80%
  - PCNL, ureteroscopy only if special circumstance: ESWL failure, anatomic obstruction → more invasive

## Chapter 99 Questions - Stone surgery.doc

- stones 10-20mm
  - ESWL first line: stone-free rate 65%
    - poor result if cysteine, lower pole
  - PCNL, ureteroscopy: stone-free rates 89% and 72% → use if stone composition, location, or renal anatomy prevent ESWL
- stones 20-30mm
  - PCNL first line, followed by ESWL if needed
  - ESWL: stone-free rate 34%, high rates (33%) of 2<sup>nd</sup> procedure if used alone
  - ureteroscopy inferior to PCNL if large stone burden: 1/3 require 2<sup>nd</sup> look, high incidence of recurrences
- stones > 30mm
  - PCNL first line regardless of size, location, composition
  - ESWL stone-free rate only 27%

### What was the 1988 NIH recommendation for treatment of stones > 2cm?

- approach w/ PCNL initially, followed if needed, w/ ESWL
- due to high retreatment rates and need for other procedures

### What is the 10-year mortality rate for pts with staghorn stones?

- untreated 28%
- treated 7.2%

### How can one classify staghorn stones?

- old system
  - partial staghorn: renal pelvic stone extending into 2 calyceal groups
  - full staghorn: extending into all major calyceal groups, filling > 80% of collecting system
- 3D reconstruction w/ CT
- stone surface area

### How does PCNL compare w/ ESWL for the treatment of staghorn stones?

- overall stone-free rate
  - PCNL +/- ESWL: 74-84%
  - ESWL alone: 22-51%

### What are the results for OSS for struvite stones?

- stone-free rate 85%
- 30% stone recurrence rate

### What are the advantages of PCNL over OSS?

- shorter procedure times
- less need for blood transfusions
- less narcotics
- rapid return to work

### What is "sandwich" therapy for stones?

- primary PCNL, followed by ESWL for inaccessible fragments, followed by 2<sup>nd</sup> PCNL
- each separated by 1-2 days

### In descending order, what stones are most resistant to ESWL?

- cystine
- brushite (calcium hydrogen phosphate dihydrate)
- calcium oxalate monohydrate
- hydroxyapatite
- struvite (MAP)
- calcium oxalate dihydrate
- uric acid

### How well can one predict stone composition from plain Xray?

- poor: 39%

### What are the options for treatment of stones in a patient w/ cystinuria?

## **Chapter 99 Questions - Stone surgery.doc**

- ESWL for stones < 15mm
- PCNL for stones > 15mm
- ureteroscopy/renoscopy for stones 15-30mm

### **How does stone shape affect reaction to ESWL?**

- smooth edged stones w/ homogenous structure need more shock waves to be fully fragmented

### **What are the options for treatment of stones associated w/ UPJO?**

- open pyeloplasty w/ stone extraction
- PCNL w/ endopyelotomy
  - treat underlying metabolic abnormalities that often are present
- retrograde endopyelotomy

### **What is the incidence of stone formation in a calyceal diverticulum?**

- 10-40%

### **What are the options for treatment of a stone in a calyceal diverticulum?**

- ESWL: stone-free rate only 21%
- PCNL: stone-free rate 93%
- laparoscopic calyceal diverticulectomy: limited to large, exophytic, peripheral diverticula in anterior calyces (difficult w/ perc)
- retrograde approach

### **What are the options for treatment of a stone in a horseshoe kidney?**

- ESWL: only if normal urinary drainage, stone < 1.5cm
- **PCNL first line:** stone-free rate 75-100%

### **How does location of stone affect results of ESWL?**

- LPS: stone-free rate 60%
- middle and upper pole: 70-90%

### **What interventions can improve LPS clearance?**

- controlled inversion therapy
- mechanical percussion and inversion
- irrigation w/ NT

### **What anatomic features of the collecting system may play a role in stone clearance?**

- angle b/w lower pole infundibulum and the renal pelvis (LIP angle)
- width/diameter of the lower pole infundibulum (IW)
- spatial distribution of the calyces (?multiple lower pole calyces)

### **How should one treat LPS?**

- LPS > 20mm
  - should be treated w/ PCNL
- LPS 10-20mm: controversial, all acceptable options
  - stone-free rates higher w/ PCNL than ESWL (73% vs. 44%)
  - morbidity higher in PCNL than ESWL or ureteroscopy
- LPS < 10mm
  - no difference b/w PCNL and ESWL
  - ESWL is preferred approach

### **What is the fate of residual fragments after stone treatment?**

- most pts have fragments in kidney few days after ESWL
- most fragments pass spontaneously after 1<sup>st</sup> 3 months
- small fragments < 4mm (CIRF – clinically insignificant residual fragments) often become symptomatic
  - 43% pts become symptomatic or require intervention
- if infection stone, 75% regrow (compared w/ 10% of pts w/ complete removal)
- if metabolic stone disease (ex: cystine), complete stone removal prolongs tx intervals

### **What are the indications for intervention for ureteral stones?**

## **Chapter 99 Questions - Stone surgery.doc**

- intractable sx
- infection
- obstruction
- stone unlikely to pass spontaneously

### **What is the most significant measurement affecting stone passage?**

- stone width

### **What is the chance of ureteral stone passage based on size?**

- < 4mm: 80%
- 4-6mm: 60%
- > 6mm: 20%

### **What is the chance of ureteral stone passage based on location?**

- proximal: 20%
- middle: 45%
- distal: 70%

### **What are the surgical options for proximal ureteral stones?**

- ESWL +/- stone manipulation
- ureteroscopy
- PCNL
- open/lap stone surgery

### **What factors affect management of ureteral stones?**

- Stone
  - location: difficult to scope past iliac vessels
  - size: stones > 8mm difficult to pass spontaneously
  - composition: most ureteral stone refractory to medical therapy
  - degree of obstruction
- Clinical
  - sx severity: caution w/ use of PGs: can decrease ipsilateral RBF
  - pt expectations
  - UTI: delay definitive tx until UTI treated
  - solitary kidney
  - abnormal ureteral anatomy
- Technical
  - equipment availability, costs

### **What are the AUA guidelines for treatment of a proximal ureteral stone?**

- stone < 1cm: ESWL +/- push back
- stone > 1cm: ESWL, PCNL, or ureteroscopy

### **Why are impacted stones more resistant to ESWL?**

- lack of a liquid interface

### **What are the indications for ureteroscopy of a proximal ureteral stone?**

- fail ESWL
- hx of cystine stones
- distal obstruction
- impacted stones
- obese pts
- coagulopathy
- ESWL not available

### **What are the results of ESWL compared to ureteroscopy for distal stones?**

- stone-free rates 81% vs. 94%
- retreatment rates 27% vs. 8%
- ESWL comparable to ureteroscopy for stones < 1cm, less efficient w/ larger stones

## **Chapter 99 Questions - Stone surgery.doc**

### **What are the advantages of ESWL and ureteroscopy for distal stones?**

- ESWL
  - effective and noninvasive
  - outpt basis w/ IV sedation
  - no stents needed if small
- Ureteroscopy
  - high chance of rendering pt stone free
  - longer time to achieve stone-free state w/ ESWL

### **What are the RF for developing bladder stones?**

- BOO
- neurogenic bladder
- chronic bacteriuria
- foreign bodies
- bladder diverticulae
- upper tract stones

### **What are the major components of most bladder stones?**

- struvite (infected)
- calcium oxalate and uric acid common (noninfected)

### **What are the contraindications to cystolitholapaxy w/ stone crushing forceps?**

- small-capacity bladder
- multiple stones
- stones > 2cm
- hard stones
- bladder stones in children
- inadequate urethras

### **What are the options for treatment of a bladder stone?**

- conservative management w/ Suby G/M solution – not appropriate
- cystolitholapaxy
- cystolithotripsy
  - EHL
  - laser
  - US
  - pneumatic lithotripter
- perc cystolithotomy
- open cystolithotomy

### **What are the problems w/ EHL?**

- may propel fragments away
- hard stones difficult
- bladder rupture 1.9%

### **What are the contraindications to percutaneous cystolithotomy?**

- hx of bladder malignancy
- prior abdo or pelvic surgery
- prior pelvic radiation
- active UTI or abdo wall infection
- pelvic prosthetic

### **What are the indications for open cystolithotomy?**

- large stone burden
- hard stones refractory to endoscopy
- abnormal anatomy
- concomitant open prostatectomy or diverticulectomy

### **What is the role of ESWL in treating bladder stones?**

- pts who are unfit for surgery

## **Chapter 99 Questions - Stone surgery.doc**

- pts that refuse surgery  
→ usually have retained fragments that require other procedures

### **What are the RF for developing stones in pts w/ urinary diversion?**

- hyperchloremic metabolic acidosis w/ hypercalciuria and hypocitraturia
- UTI w/ urea-splitting organism
- incomplete diversion emptying
- FB (staples)
- mucus production

### **What is the incidence of stone formation in diversions?**

- nonrefluxing colon conduits 3%
- sigmoid conduits 4%
- ileocecal conduits 5%
- transverse colon conduits 11%
- ileal conduit 4-20%
- Indiana pouch 3-13%
- Kock pouch 4-43%

### **What is the difference in urinary characteristics b/w Kock and Indiana pouches?**

- hypocitraturia more common in Indiana pouch group than Kock pouch
- no difference b/w Ca, P, Mg excretion

### **Why does the Kock pouch have such a high incidence of stone formation?**

- construction w/ staples
- previous Marlex mesh collars for afferent nipple valve

### **What are the sx of stones in diversions?**

- gross hematuria
- pressure sensation in diversion
- difficult catheterization
- increased frequency catheterization
- mild UI
- lower abdo discomfort
- recurrent UTI

### **What are the indications for open surgical removal of a stone in a diversion or augment?**

- inability to perform perc/trans-stomal removal
- failed endourologic management
- concomitant open surgery planned on diversion
- large stone burden
- multiple stones w/ anticipated long operative times

### **What measures can be taken to prevent formation of stones in diversions?**

- regular evacuation of the reservoir
- daily irrigation w/ NS or tap water
- eradication of urea-splitting organisms
- routine surveillance w/ endoscopy

### **When do most pts w/ stones in pregnancy present?**

- during 2<sup>nd</sup> or 3<sup>rd</sup> trimester

### **What is the etiology of hydronephrosis during pregnancy?**

- increased levels of progesterone  
→ causes relaxation of smooth muscle, reducing peristalsis
- mechanical compression of the ureters from the enlarging uterus
- 30-50% increase in GFR and RPF

### **What physiologic changes in pregnancy can change predisposition to forming renal stones?**

- pregnancy induces state of absorptive hypercalciuria and mild hyperuricosuria



## Chapter 99 Questions - Stone surgery.doc

- increased excretion of urinary inhibitors: Mg, citrate
- increased UO
- accelerated encrustation of stents during pregnancy

### What are the sx of stones in pregnancy?

- flank pain
- hematuria: can occur in normal pregnancy
  - **pyuria common in normal pregnancy: not a good indicator**
- UTI
- LUTS
- N/V, F/C

### What is the radiation dose below which no adverse effects occur to the fetus?

- greatest risk in 1<sup>st</sup> trimester
- 5-15 rads
  - KUB = 0.2 rads
  - IVP = 0.4-1.5 rads

### How well does conservative management work in pregnant pts w/ stones?

- conservative management results in spontaneous stone passage in 50-80%
- intervention in 1/3: for pain uncontrolled by analgesia

### What are the contraindications to ESWL?

- Absolute
  - pregnancy
  - uncorrected coagulopathy (D/C NSAIDs, coumadin, heparin)
- Relative
  - UTI (pretreatment with antibiotics, periprocedural antibiotics, stenting)
  - children (needs gantry modification due to size)
  - obese patients (weight limit to machine, difficulty with imaging stone)
  - obstruction distal to stone (stent)
  - cardiac pacemaker (cardiology available if transvenous pacemaker needed)
  - renal artery calcification and AAA (care to avoid with shock waves)
  - poor body habitus, severe orthopedic deformities (may be unable to position)
  - poor renal function: serum creatinine > 3 mg/dl
  - uncontrolled hypertension (increased bleeding risk)

### How can one classify lithotriptors?

- Intracorporeal
  - Flexible
    - EHL (electrohydraulic)
    - Laser
  - Rigid
    - Ballistic
    - Ultrasonic
- Extracorporeal
  - Electrohydraulic (Spark-Gap)
  - Electromagnetic
  - Piezoelectric

### How does EHL work?

- fragments stones w/ shock waves generated by an underwater electrical discharge
- underwater spark plug w/ 2 concentric electrodes of different voltage polarities separated by insulation
- current supplied to overcome insulative gap → spark produced
- spark discharge causes explosive formation of a plasma channel and vaporization of the water surrounding the electrode
- rapidly expanding plasma causes hydraulic shock wave, then cavitation bubble formation
- collapse of cavitation bubble causes strong secondary shock wave, leading to formation of high-speed microjets
- shock wave not focused

### What are the advantages and disadvantages of EHL?

## **Chapter 99 Questions - Stone surgery.doc**

- Disadvantages
  - narrow margin of safety due to risk of ureteral perforation → expansion of cavitation bubble
  - high risk of perf w/ impacted stones
  - retrograde propulsion of stones
- Advantages
  - cheapest intracorporeal device
  - successful in 90% → rough stones break easily
  - flexibility of probes

### **What is the success rate of EHL?**

- 90% successful fragmentation

### **What is ballistic lithotripsy?**

- "jackhammer" lithotripsy: metal projectile in the handpiece of the lithoclast is propelled by measured bursts of compressed air against the head of a metal probe at 12 Hz

### **How does ultrasonic lithotripsy work?**

- apply electrical energy to excite a piezoceramic plate located in the US transducer
- plate resonates at a specific frequency and generates ultrasonic waves at a freq of 23000-25000Hz
- U/S energy transformed into longitudinal and transverse vibrations of the hollow steel probe
- probe tip causes the stone to resonate at high frequency and break

### **How does laser lithotripsy work?**

- pulse laser results in very high power density at stone surface
- causes release of electrons and formation of a "plasma" bubble
- expansion then collapse of the bubble creates a shock wave that is responsible for stone formation
  - Holmium laser: produces elongated cavitation bubble that generates only a weak shock wave
  - lithotripsy occurs primarily through photothermal mechanism that causes stone vaporization

### **What are the advantages and disadvantages of laser lithotripsy?**

- Advantages
  - safer and more efficient
  - ability to fragment all stones
  - smaller stone debris → easily irrigated
  - decreased chance of retropulsion
  - reusable fibers
- Disadvantages
  - high initial cost
  - production of cyanide when uric acid stones treated → not significant

### **What are the advantages and disadvantages of ballistic lithotripsy?**

- wide margin of safety
  - low risk of ureteral perforation
- success rate similar to EHL
- stones easily pinned down
- no disposable costs, long life of probes
- high rate of retropulsion
- significant power loss w/ bowing of probe

### **How does the US lithotripter work?**

- application of electrical energy to excite a piezoceramic plate in ultrasound transducer
- plate resonates at a specific frequency and generates ultrasonic waves at 23-25kHz
- transformed into longitudinal and transverse vibrations of the hollow steel probe, transmitting energy to the stone
- causes stone to resonate at high frequency and break

### **What are the advantages and disadvantages of US lithotripsy?**

- efficient combination of fragmentation and fragment removal
  - stones removed continuously w/ suction
- minimal damage to tissues, minimal heat creation
- flow of fluid cools instrument

## **Chapter 99 Questions - Stone surgery.doc**

- rigid probe, small diameter

### **How does the electrohydraulic (spark-gap) ESWL lithotripter work?**

- spherically expanding shock wave generated by underwater spark discharge
- explosive vaporization of water at shock tip
- ellipsoidal reflector bounces spherically expanding shock waves to focus
  - electrode placed at F1 and target placed at F2 → majority of energy focused at F1

### **How does the electromagnetic lithotripter work?**

- produce a plane or a cylindrical shock wave
  - plane waves focused by an acoustic lens
  - cylindrical waves are reflected by a parabolic reflector and transformed into a spherical wave
- electrical current sent through 1 or both of conductors, producing magnetic field produced b/w conductors

### **How does the piezoelectric generator work?**

- mosaic of polarized polycrystalline ceramic elements
  - each can be caused to rapidly expand by application of a high-voltage pulse
- placed on the inside of a spherical dish to permit convergence of a shock front

### **Which model of lithotripter remains the gold standard?**

- unmodified Dornier HM3

### **What are the potential mechanisms for stone breakage from ESWL?**

- compression fracture: large +ve pressures generated by the shock wave on the front face of the stone
- spallation: large -ve pressures from waves that reflect from the back of the stone that put stone under tensile stress
- acoustic cavitation: formation and behaviour of bubbles
  - bubbles form, fill w/ vapour, and collapse → high pressure and temp
  - liquid jet forms (aka cavitation microjet) forms inside bubble during collapse → accelerates to high speed
- dynamic fatigue: nucleation, growth, and coalescence of flaws w/i the stone caused by tensile or shear stress

### **What are the side effects of ESWL?**

- Extrarenal
  - hematuria
  - gastric or duodenal erosion → most common extrarenal injury
  - lung injury
  - hematochezia (colon mucosal damage)
  - MI
  - stroke
  - brachial plexus palsy
- Intrarenal
  - subcapsular hematoma
  - renal hemorrhage
  - edema

### **What are the RF for developing acute renal side effects after ESWL?**

- age: children and elderly
- obesity
- coagulopathies
- solitary kidney
- thrombocytopenia
- DM
- CHF
- hypertension
- increased thromboplastin time
- use of ASA

### **What are the changes seen in the kidney after lithotripsy?**

- dilation of veins, w/ endothelial damage and thrombus formation
- decrease in plasma flow
- increased RI

## Chapter 99 Questions - Stone surgery.doc

### What are the long-term potential side effects of ESWL?

- increased BP
- decreased renal function
- increased rate of stone recurrence

### What are the acute and chronic histologic changes seen in kidneys after ESWL?

- Acute
  - venous thrombi
  - mild tubular necrosis
  - tubular dilation and cast formation
  - damaged veins and small arteries
  - rupture of glomerular and peritubular capillaries
- Chronic
  - nephron loss
  - dilated veins
  - streaky fibrosis
  - diffuse interstitial fibrosis
  - Ca and hemosiderin deposits
  - hyalinized and acellular scars from cortex to medulla

### At which location does hemorrhage occur after ESWL?

- perirenal, subcapsular, or intraparenchymal
  - always at or near F2

### What factors increase the degree of renal trauma in animals?

- number of shocks
- period of shock wave administration (less time = more damage)
- accelerating voltage (higher voltage increases damage)
- type of shock-wave generator
- kidney size
- preexisting renal impairment

### What is the only absolute contraindication to PCNL?

- uncorrected coagulopathy

### What are the factors to be considered when choosing renal access for PCNL?

- ideal subcostal tract begins inside posterior axillary line, transversing renal parenchyma at posterolateral aspect of kidney
  - puncture through upper tract dangerous → hit posterior branch
  - avoid direct puncture to calyx
- approach below 12<sup>th</sup> rib if possible to avoid pleural injury
  - supracostal puncture performed only during full expiration
- puncture too laterally may injure colon
- lower pole puncture associated w/ fewer complications
- solitary calyceal stone: preferred approach directly into calyx w/ stone

### In which group of patients should one be wary of posterior colonic displacement for a PCNL?

- thin female pts w/ little retroperitoneal fat
- elderly patients
- pts w/ jejunoileal bypass w/ enlarged colon

### What factors increase the risk of colon injury during PCNL?

- anterior calyceal puncture
- previous extensive renal operation
- horseshoe kidney
- kyphoscoliosis

### What are the indications for a supracostal puncture?

- predominant amount of stone in upper calyces
- associated UPJO requiring endopyelotomy

## **Chapter 99 Questions - Stone surgery.doc**

- multiple lower pole infundibula and calyces w/ stones
- ureteral stone
- staghorn w/ substantial upper pole stone burden
- horseshoe kidneys

### **What are the indications for multiple punctures for PCNL?**

- any calyx contains stones larger than 2cm and unreachable through primary access point w/ rigid scope
- stones < 2cm, cannot be reached w/ flexible instrument
- Y puncture: stone in adjoining calyx cannot be reached w/ flexible nephroscope

### **What is a "mini-perc?"**

- 11-15F peel-away tract instead of 24-30F sheath
- used for stones < 2cm, 6.9F semi-rigid ureteroscope

### **What are the indications for a nondilated puncture in PCNL?**

- eccentrically placed calyx encountered that is difficult to locate through established access  
→ 2<sup>nd</sup> puncture into desired calyx w/o tract dilation, instill methylene blue or gas bubbles or wire
- insertion of small NT

### **What is the appropriate height of irrigant above pt during PCNL?**

- 80cm, to keep intrapelvic pressure low and prevent fluid absorption

### **What are the best sites for access for PCNL in a horseshoe kidney?**

- upper poles: **are posterior and lateral**
  - inside posterior axillary line just superior to 12<sup>th</sup> rib
  - angle inferiorly
  - most calyces point dorsomedially or dorsolaterally
- all blood vessels enter kidney ventrally and medially
- may be associated w/ retrorenal colon → get pre-op CT

### **What is the incidence of calculi in renal transplant pts?**

- 0.5-3%

### **What are the RF for stones in transplant pts?**

- metabolic abnormalities
- foreign bodies: sutures, stents
- recurrent UTI
- papillary necrosis

### **What is the best position for puncture into a transplant kidney?**

- renal pelvis located medially, so posterior calyces point anteriorly  
→ anterior approach similar to posterior approach to native kidneys
- pt in lithotomy
- access most safely established into lower pole w/ skin puncture as caudal as possible

### **What are the complications of PCNL?**

- bleeding: 1-10%
  - AV fistula
  - pseudoaneurysm
- sepsis 0.3-2.5%
- adjacent organ injury: bowel, spleen
- failed access: <5%
- perf of renal pelvis or ureter: <2%
- pneumothorax
- pleural effusion
  - if supracostal: 4-12%
- failure of equipment
- mortality: 0.05-0.3%

### **What are the transfusion rates for PCNL?**

## Chapter 99 Questions - Stone surgery.doc

- 1-10%

### How can one deal w/ excessive bleeding during PCNL?

- cessation of procedure
- placement of NT
- clamp NT x 10min to allow for tamponade
- Kaye nephrostomy tamponade balloon catheter
- angiography and embolization
- nephrectomy: partial

### What is the tx of colonic injury during PCNL?

- place ureteral catheter or stent
- withdraw NT to colon: colostomy tube
- leave colostomy tube x 7d, remove after nephrostogram

### What are the RF for steinstrasse?

- large stone burden
- staghorn stone
- bilateral ESWL
- pre-existing ureteral obstruction

### How often does steinstrasse occur in stented patients?

- 1-2cm: 4%
- 2-3cm: 14%
- >3cm: 30%

### How often does steinstrasse clear spontaneously?

- 60-80% → can be observed initially

### What are the complications of ureteral stone management?

- Intra-op
  - ureteral avulsion
  - perforation
  - false passage
  - failure to gain access
  - iliac artery injury
  - submucosal wire placement
  - submucosal stone
  - lost stone: manipulated into position outside ureter → usually harmless
- Postop
  - ureteral trauma
    - iatrogenic injury
  - retained stone fragments
  - ureteral stricture
    - causes: radiation, initial balloon dilation, mucosal tears, extravasation, thermal injury secondary to intraureteral lithotripsy
  - reflux
  - sepsis
  - death

### Which modality of treatment has the highest rate of stone perforation?

- EHL

### What are the indications for ureteroscopy and stone manipulation?

- failed ESWL (single stone < 1cm or multiple stones < 5mm)
- radiolucent stone (<1.5cm)
- concomitant renal and ureteral stones
- intrarenal stenosis
- nephrocalcinosis
- urinary diversion

## Chapter 99 Questions - Stone surgery.doc

- need for complete stone removal (ex: pilots)
- bleeding disorder
- failure of stone passage spontaneously after 3-4weeks

### What are the results for ureteroscopy for renal stones stratified by location?

- lower pole: 84%
- middle pole: 93%
- upper pole: 100%

### What are the indications for open removal of ureteral/renal calculi?

- stone burden too complete for PCNL
  - depends on MDs judgement
- salvage procedure
- planned abdominal operation coincides w/ symptomatic ureteral stone episode
- associated anatomic abnormality requiring open repair
  - UPJO
  - infundibular stenosis
  - ureteric abnormality

### What are the complications of ESWL?

- Complications related to stone fragmentation
  - residual stones
    - due to stone composition (COM, cysteine most difficult), size, location, poor localization
  - steinstrasse, obstruction
  - infectious complications
    - bacteremia in up to 14%
    - recurrent UTI if infection stones remain
    - perinephric abscess
    - endocarditis
    - military TB
    - death
- Complications related to tissue effects of ESWL
  - renal complications
    - gross hematuria
    - hematoma: subcapsular, perirenal, retroperitoneal, parenchymal → usually resolve in 6/12
    - perirenal fluid collection
    - renal enlargement
    - renal fracture
    - loss of corticomedullary differentiation
    - hypertension: 1-8% new onset
    - decreased renal function
    - RPF
  - nonrenal complications
    - Vascular: rupture of AAA → **caution!**
    - Cardiac: arrhythmia
    - Other: splenic injury, colonic injury, ureteral edema, ureterocolonic fistula, ureterovaginal fistula, urinoma, autonomic dysreflexia
    - ureteral perforation with stent
      - ◆ May use ESWL for large leading fragment or ureteroscopy
    - ureteral complications
      - ◆ stricture
      - ◆ ureteral trauma
    - lung – hemoptysis
    - pancreatitis
    - GI erosion
    - elevated LFT's
    - biliary colic with fragmentation of biliary stones



**Chapter 101**  
**• The Adrenals •**

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**What is the max adrenal size and when is it achieved?**

- 5-10g, achieved at birth, then rapidly regresses  
→ fetal adrenal cortex regresses rapidly during 1<sup>st</sup> 6 wks of life

**Describe the vascular supply to the adrenal.**

- arterial: inferior phrenic, additional branches from aorta and renal artery  
→ adrenal arterial supply from gonadal in 60%
- venous: common vein on R, exiting apex and entering posterior IVC  
→ L adrenal vein empties into L renal vein  
→ L inferior phrenic vein communicates w/ adrenal vein

**Describe the embryologic origin of the adrenal.**

- adrenal cortex develops from mesoderm
- adrenal medulla develops from neuroectoderm
- during 5<sup>th</sup> week, mesothelial cells b/w the root of the mesentery and the developing gonad proliferate and invade the mesenchyme to form adrenal cortex
- adrenal medulla derived from cells of the neural crest that migrate at 7<sup>th</sup> week to form collections that enter fetal cortex

**What is the hormone product of the adrenal cortex?**

- glomerulosa: aldosterone (mineralocorticoid)
- fasciculata and reticularis: cortisol, DHEA, DHEAS, androstenedione

**What is the protein precursor to ACTH, and what other proteins are derived from it?**

- POMC: pro-opiomelanocortin  
→ beta-lipotrophin, alpha-melanocyte stimulating hormone, beta-melanocyte stimulating hormone, beta-endorphin, methionine enkephalin

**What abnormality in cortisol production is a critical finding in Cushing's?**

- lack of diurnal variation

**What is the primary physiologic control of aldosterone?**

- angiotensin II

**List the hormonal stimuli for ACTH release.**

- CRH
- vasopressin, oxytocin, epi, AII, VIP, serotonin, gastrin-releasing peptide, ANF, GABA

**Describe the physiologic control of aldosterone secretion.**

- decreased renal perfusion → renin release → AII formation → aldo secretion  
→ primary control
- increased potassium → increases adrenal ability to make aldo  
→ less potent stimulus

**What are the functions of glucocorticoids?**

- accumulation of glycogen in liver and muscle to enhance skeletal and cardiac muscle contraction
- increase vascular contractility and decrease permeability → help to maintain BP
- impaired peripheral glucose utilization
- cause protein catabolism: excess causes muscle wasting and myopathy
- inhibit bone formation: excess causes osteopenia
- inhibit collagen synthesis: excess impairs wound healing
- has anti-inflammatory activity



## Chapter 101 Questions - Adrenal.doc

- has anti-immune system activity: immune-mediated inflammation
- maintains normal GFR

### What is the function of aldosterone?

- maintains Na and K balance
  - stimulates Na absorption and increased K and H secretion
  - 95% of adrenal mineralocorticoid activity

### What are the active sites of aldosterone?

- kidney, gut, salivary glands, sweat glands

### What % of cortisol is bound, and to what?

- corticosteroid-binding globulin: 80%
- albumin: 10-15%
- free: 7-10%

### Which tests can be used to diagnose adrenal carcinoma?

- plasma DHEAS level is most accurate → most often used
- plasma cortisol
- urinary-free cortisol
- elevated DHEA, androstenedione, 17-ketosteroids out of proportion to glucocorticoid production

### What tests are used to diagnose women with adrenal pathology?

- increased T, increased DHEA

### What is the T<sub>1/2</sub> of aldosterone?

- 20-30 minutes

### What is secreted by the adrenal medulla, in what proportion, and by which cells?

- epi (14%), NE(73%), dopamine(13%)
- secreted by chromaffin cells

### What is the origin of the term *chromaffin* cell?

- cells stain brown when exposed to chromium salts, due to oxidation of epi and NE

### Describe the enzymatic pathway for catechol synthesis and where it occurs.

- phenylalanine → tyrosine → dopa → dopamine → NE → epi
- occurs in adrenal, CNS, and adrenergic nerve terminals

### What is the T<sub>1/2</sub> for catecholamines?

- < 20 seconds

### What are the metabolites of catechols?

- epi/NE → metanephrine/normetanephrine via catechol-O-methyltransferase (COMT)
- metanephrine/normetanephrine → MOPGAL, epi/NE → DOPGAL via monoamine oxidase (MAO)
- primary metabolite in urine is vanillylmandelic acid (VMA)
  - also have metanephrine, normetanephrine

### Describe the locations of each of the adrenergic receptors.

- $\alpha$ 
  - $\alpha_1$ 
    - postsynaptic agonists
    - vascular smooth muscle: vasoconstriction
    - prostate: contraction
    - liver: glycogenesis
  - $\alpha_2$ 
    - presynaptic: inhibit NE release
    - postsynaptic agonists
    - large veins: vasoconstriction
    - brain: decrease sympathetic outflow

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- pancreas: inhibit insulin release
- gut: relaxation
- adipocyte: inhibit lipolysis
- $\beta$ 
  - $\beta_1$ 
    - heart: +ve inotrope and chronotrope
    - adipocyte: lipolysis
    - kidney: stimulate renin release
  - $\beta_2$ 
    - lung: bronchodilation
    - vascular smooth muscle: vasodilation
    - liver: gluconeogenesis
    - uterus: relaxation
    - gut: relaxation
- Dopaminergic
  - $D_1$ 
    - vascular: vasodilation
  - $D_2$ 
    - presynaptic: inhibit NE release

### What is Cushing's syndrome?

- symptom complex caused by excess circulating glucocorticoids

### What are the causes of Cushing's syndrome?

- exogenous source of steroid
  - therapeutic steroid
- adrenal adenoma or carcinoma
- micro/macronodular hyperplasia
- pituitary hypersecretion of ACTH (corticotropin)
- Cushing's disease (75-85%) = pituitary adenoma w/ increased ACTH secretion
- ectopic secretion of ACTH or CRH
- Pseudo-Cushing's syndrome
  - depression, alcoholism

### What are the potential sources for ectopic ACTH?

- lung ca: 50%
- pancreas ca: 10%
- thymoma: 10%
- bronchial adenoma: 5%
- pheo
- thyroid ca, liver ca, prostate ca, ovarian ca
- mediastinal ca, breast ca, parotid ca, esophageal ca
- paraganglioma, ganglioma

### What are the presenting sx of Cushing's?

- obesity
- cachexia
- hypertension
- diabetes
- centripetal adiposity / weight gain
- weakness
- muscle atrophy
- hirsutism / virilization
- menstrual abnormalities
- purple striae
- moon facies
- osteoporosis
- early bruising
- acne / skin pigmentation
- hypokalemic alkalosis

## Chapter 101 Questions - Adrenal.doc

- mental changes
- edema
- headache
- poor healing
- growth retardation

### What is the best test to diagnose elevated cortisol levels?

- 24-hr excretion of cortisol is most direct and reliable index of cortisol secretion

### What are the causes of pseudo-Cushing's?

- alcoholism
- depression

### What are the sx of subclinical Cushings?

- 1 -dx Cushings syndrome
  - increased 24h free cortisol ( $> 3 \times$  upper limit of normal)
  - 1mg ON DST (cortisol  $> 138$  nmol/l)
    - if don't suppress w/ 1mg, have dx of Cushing's syndrome
2. -look for cause of cushing's syndrome
  - decreased ACTH
  - high dose 8mg DST: cortisol not decreased
  - CRH test: cortisol same
- 3.- imaging: adrenal tumour or hyperplasia on CT
  - hyperplasia can be caused by pituitary tumour

### Describe the algorithm used to diagnose Cushing's syndrome and its causes.

- 2-3 24 hr urine collections for cortisol: either normal, Cushing's, or equivocal
  - normal: rise in plasma ACTH and cortisol in morning, fall in evening
  - equivocal: **low-dose dexamethasone suppression test**
    - 1mg dexamethasone PO x 1, test cortisol in am (0.5mg PO q6h x 2d is old test) → causes dramatic fall in 17-hydroxysteroid, urinary free cortisol, plasma cortisol
      - ◆ ?less reliable than 2d test in obese pts
    - equivocal: midnight plasma cortisol, CRH-dexamethasone, or naloxone test
- 2-3 late afternoon or midnight plasma ACTH and cortisol measurements
  - No Cushings
  - ACTH-independent Cushing's (high cortisol, low ACTH: primary adrenal Cushing's syndrome)
    - get adrenal CT or MRI → surgery
  - ACTH-dependent Cushing's (high cortisol, high ACTH: Cushing's disease or ectopic ACTH or CRH syndrome)
    - perform **high-dose dexamethasone suppression test** if serum ACTH not available
      - ◆ 8mg PO x 1 (old test: 2mg PO q6h x 2d) → measure urine and plasma cortisol
        - ◆ pituitary disease: should be 50% or more suppression in cortisol → some -ve feedback
        - ◆ adrenal adenoma or ca: no suppression of cortisol secretion
    - metyrapone stimulation test
      - ◆ metyrapone blocks conversion of 11-desoxycortisol → cortisol
      - ◆ cortisol level falls, ACTH increases, urinary 17-ketosteroid levels increase
    - petrosal venous sinus sampling → most direct way to show ACTH hypersecretion
      - ◆ measure levels of ACTH in venous blood

### What does adrenal hyperplasia appear as on CT?

- diffuse thickening and elongation of adrenal rami
- nodular cortical hyperplasia in 10-20%: small, bilateral, multiple nodules ( $< 2$ cm)

### What distinguishes adrenal adenoma on CT from other lesions?

- adenoma
  - sharp margins
  - $< 5$ cm
  - smooth contour
  - lack of growth
  - homogenous

## Chapter 101 Questions - Adrenal.doc

- < 10 HU
- mets
  - larger
  - less well-defined
  - not homogenous
  - thick irregular enhancing ring
  - HU: not determinate
- carcinoma
  - often indistinguishable
  - necrosis and calcification more common in carcinoma
  - carcinomas somewhat larger size (>6cm) than adenomas
  - adenomas usually >2cm, solitary, w/ contralateral adrenal atrophy, HU < 10
- hemorrhage: enhancing ring

### What is the treatment of Cushing's disease and ectopic ACTH syndrome?

- ectopic ACTH: treat primary tumour
- block secretion of functional steroids: adrenolytics
  - aminoglutethimide: blocks cholesterol → pregnenolone
  - metyrapone: blocks 11-desoxycortisol → cortisone
  - ketoconazole: blocks cytochrome P450 side-chain cleavage in steroid synthesis → fastest acting
  - mitotane (ortho-para-DDD)
- block cortisol receptor: mifepristone
- bilateral adrenalectomy w/ steroid replacement
- transsphenoidal hypophyseal microsurgery: most effective and safest treatment of Cushing's disease
- radiation

### What is Nelson's syndrome and how is it treated?

- pituitary tumours (chromophobe adenomas) post-adrenalectomy w/ hyperpigmentation
- treated w/ primary radiation

### What is the mechanism of Cushing's syndrome during pregnancy?

- during normal pregnancy, plasma cortisol binding protein and plasma protein bound and unbound cortisol levels rise
- resistance to dexamethasone suppression that progresses w/ each trimester

### What is the treatment of adrenal adenoma during pregnancy?

- surgical removal
- metyrapone
- low placental transfer: fetus not affected and requires no treatment

### What is the incidence of adrenal carcinoma?

- very rare: 1 in 1.7 million

### How can one classify adrenal carcinoma?

- Functional
  - Cushing's syndrome
  - Virilization in females
    - increased DHEA, 17-ketosteroids (better test)
    - increased T
  - Feminization in males
  - Hyperaldosteronism
  - Mixed
- Nonfunctional

### What is the usual size cutoff for adrenal carcinoma?

- usually > 6cm (105 of 114)

### Describe the approach to an incidentally found adrenal mass.

- determine if functional adrenal mass
  - rule out pheo (urinary VMA, metanephrine)
  - rule out hyperaldosteronism (K level if hypertensive)

## Chapter 101 Questions - Adrenal.doc

- glucocorticoid evaluation if clinical stigmata of Cushing's: 24h urine cortisol, serum ACTH/cortisol, dexamethasone testing
- determine size on CT
  - > 5cm and solid: OR
    - no need to bx if solid: cannot distinguish b/w adenoma and carcinoma on bx
    - cystic: ?needle biopsy
  - < 5cm: MRI
    - high signal T2: OR
    - low signal T2 (?adenoma): follow w/ CT q6mo
      - ◆ if enlarging, repeat functional tests and remove if suspicious
  - FNA well tolerated

### What is the differential for the incidentally found adrenal mass?

- Benign
  - cyst
  - hemorrhage
  - myelolipoma
  - adenoma +/- secretory (pheo, Cushing's)
    - testosterone secreting adrenal cortical tumours
  - hyperplasia
  - oncocytoma
- Malignant
  - Primary: adrenal carcinoma, estrogen secreting adrenal cortical tumours, aldo-secreting carcinoma
    - Functional
      - ◆ Cushing's syndrome
      - ◆ Virilization in females
        - ◆ increased DHEA, 17-ketosteroids (better test)
        - ◆ increased T
      - ◆ Feminization in males
      - ◆ Hyperaldosteronism
      - ◆ Mixed
    - Nonfunctional
  - Secondary

### What is the differential for bilateral masses?

- mets
- lymphoma
- infx
- hemorrhage
- CAH
- pheo

### What is the accuracy of FNA for adrenal biopsy?

- 28% nondiagnostic
- if diagnostic, specificity > 95%

### What is the DDx of a high intensity T2 lesion on MR?

- adrenal ca
- neural tumours
- mets to adrenal
- hemorrhage

### How can one determine if an adrenal mass is malignant?

- Hx/Px
- MR/CT: size, shape, heterogeneity, soft tissue density, growth over time
- Hormonal: high androgens
- FNA: only reason to do is if have primary ca elsewhere

### What are the characteristics of adrenal myelolipoma and how does it present?

- usually <5cm, unilateral, asymptomatic, and benign → follow

## **Chapter 101 Questions - Adrenal.doc**

- hematopoietic and fatty elements
- usually presents w/ pain

### **In order of descending frequency, the adrenal is the site of mets from which cancers?**

- melanoma and carcinoma of breast and lung: seen in > 50%
- RCC: 40%
- carcinoma of contralateral adrenal, bladder, colon, esophagus, gallbladder, liver, pancreas, prostate, stomach, uterus

### **Which symptoms of Cushing's are seen more frequently in carcinoma vs. adenoma of adrenal?**

- virilization w/o evidence of cortisol excess seen more in carcinoma
- hirsutism: more in carcinoma
- 17-ketosteroid and DHEAS levels: higher in carcinoma
- thin skin, purple striae, thin hair, temporal hair loss: more in adenoma

### **What are the characteristics of feminizing adrenal cortical tumours in men?**

- usually in men 25-50yrs
- larger, more palpable, highly malignant (80%) compared w/ T secreting adrenal tumours  
→ 50% die in 18mo
- pts present w/ gynecomastia, testicular atrophy, ED, decreased libido, infertility, oligospermia
- secrete androstenedione, which is converted peripherally to estrogen

### **What are the most common site of mets for adrenal carcinoma?**

- lung, liver, LN
- bone, pleura, heart

### **What is the management for adrenocortical carcinoma?**

- surgical removal of primary, +/- en bloc resection of adjacent structures and LN
- radiation: not useful
- adrenolytic drugs: mitotane (ortho-para-DDD), ketoconazole, metyrapone, aminoglutethamide  
→ mitotane: DDT derivative w/ significant GI, neurologic, dermatologic toxicity
- cis-platin, etoposide

### **What is the DDx for an adrenal cyst?**

- endothelial or lymphangiomatous cyst (45%)
- pseudocyst (39%): previous adrenal hemorrhage
- parasitic cyst: echinococcus (7%)
- true epithelial cyst (9%)

### **What is Addison's disease?**

- adrenal insufficiency

### **What is the most common cause for Addison's?**

- either TB or adrenal atrophy

### **What are the etiologies for Addison's?**

- adrenal atrophy
- Neoplastic  
→ malignant infiltration, mets
- sarcoid
- Infectious  
→ TB  
→ histoplasmosis, blastomycosis, coccidiomycosis
- Medications  
→ acute withdrawal of steroids  
→ medications causing impaired adrenal steroidogenesis: aminoglutethimide, ketoconazole, mitotane, suramin
- hemorrhagic necrosis w/ anticoagulation
- sepsis

### **What are the sx of chronic Addison's and acute adrenal insufficiency?**

- Addisons: vague sx

## Chapter 101 Questions - Adrenal.doc

- weakness, tired, fatigue
- wt loss
- anorexia
- N/V
- abdo pain
- diarrhea
- muscle pain
- salt craving
- orthostatic hypotension, dizziness, syncope
- lethargy
- Acute adrenal insufficiency
  - severe clinical deterioration
  - **fever (70%)**
  - N/V
  - abdo pain → due to adrenal hemorrhage
  - hypotension
  - abdo distension
  - lethargy, obtundation
  - hyponatremia, hyperkalemia (due to decreased aldosterone)

### What are the most common lab abnormalities in a pt w/ Addison's?

- **hyponatremia and hyperkalemia** → due to hypoaldosteronism
  - classic triad: hyponatremia, hyperkalemia, azotemia
- hypercalcemia
- hyperthyroid or hypothyroid
- DM
- gonadal dysfunction

### What is the best test to diagnose Addison's?

- rapid ACTH test
  - plasma cortisol levels measured before and 60min after 0.25mg cosyntropin IV or 100ug of CRH given

### What is the treatment of adrenal insufficiency?

- Emergency treatment
  - IV NS or D5W 2-3L ASAP, monitor for fluid overload
  - dexamethasone (Decadron) 4mg IV or hydrocortisone (Solu-Cortef) 100mg IV
  - supportive measures prn
  - no mineralocorticoids, ACTH useless
- After pt stable
  - IV NS at lower rate x 48h
  - search for reasons of adrenal crisis
  - short ACTH stimulation test to confirm dx of adrenal insufficiency
  - taper steroids over 3d
  - start mineralocorticoid replacement w/ fludrocortisone (Florinef) 0.1mg PO OD after NS stopped
- Chronic adrenal insufficiency
  - 30mg hydrocortisone + 0.05-0.1ug fludrocortisone PO OD

### What is the usual cause of selective adrenal insufficiency?

- hyporeninemia or functional hypoaldosteronism due to tubular insensitivity to normal ald levels

### What is Conn's syndrome?

- primary hyperaldosteronism
  - htn, hypokalemia, hypernatremia, alkalosis, periodic paralysis
  - due to aldosterone secreting adenoma

### What is the phenomenon of "renal escape?"

- when ald is secreted in extremely high amounts, DCT absorbs additional Na
- after gain of 1.5kg fluid, diminished proximal tubular reabsorption of sodium
  - associated w/ increased renal arterial pressure and increased ANF
  - limits the sodium retention that would normally occur w/ hyperaldosteronism

## Chapter 101 Questions - Adrenal.doc

- explains mild htn, absence of edema, and rarity of malignant htn
- a.k.a. "mineralocorticoid escape"

### What features of Conn's identify autonomous production of aldosterone?

- limited stimulation of aldo production by increasing AII levels (either by NS IV, postural stimulation)
- increased levels of aldo biosynthetic precursors: 18-hydroxycorticosterone-to-cortisol ratio
- elevated levels of weird steroids: 18-hydroxycortisol and 18-oxocortisol

### How can one differentiate primary vs. secondary hyperaldosteronism?

- PRA levels
  - increased in secondary: usually due to renal arterial or parenchymal disease
  - decreased in primary: remains low even if give Lasix

### What is AII-responsive APA (aldosterone producing adenoma)?

- variant of aldosterone producing adenoma
  - aldo production is stimulated by RAA system
  - composed of primarily glomerulosa-like cells
  - after adrenalectomy, AII infusion does not stimulate aldo release

### What is the DDX of hyperaldosteronism?

- Primary
  - PAH (primary adrenal hyperplasia)
  - adrenal adenoma
  - adrenal carcinoma
  - glucocorticoid-remediable aldosteronism (GRA, or FHI)
  - familial primary aldosteronism (FHII)
- Secondary
  - decreased effective circulating volume: cirrhosis, renal failure

### What is PAH?

- primary adrenal hyperplasia
  - adrenal glands are hyperplastic: no identifiable adrenal adenoma
  - unilateral adrenalectomy correct abnormalities

### What is GRA?

- glucocorticoid-remediable aldosteronism
  - AD form of mineralocorticoid hypertension
  - aldo biosynthesis is regulated by ACTH and not RAA

### How is GRA diagnosed and treated?

- clinical features: early-onset htn, may be complicated by cerebral hemorrhage or aortic dissection, FHx htn
- low PRA level, other evidence of aldo excess
  - hyperplasia of zona fasciculata
- overproduction of 18-OHcortisol, 18-oxocortisol
- treat w/ low dose exogenous glucocorticoid: inhibits ACTH, suppresses aldo production, normalizes PRA, corrects htn
  - a.k.a. FHI

### What is FHII?

- familial primary aldosteronism
  - aldo production not suppressed by exogenous glucocorticoid

### What are the clinical characteristics of hyperaldosteronism?

- primarily due to elevated body sodium and deficit in potassium
  - nocturia, frequency, muscular weakness, frontal headaches, polydipsia, paresthesias, visual disturbances, temporary paralysis, cramps, tetany
  - absent/mild sx if pt normokalemic, or when eating a low-salt diet

### What is the most common cause for hyperaldosteronism?

- APA in 63%
  - suspect primary aldosteronism



## Chapter 101 Questions - Adrenal.doc

- if aldo > 400 and  
ratio aldo/renin is:
  - > 550-750 if measure PRA
  - > 140 if measure plasma renin mass

### Describe the algorithm for diagnosis and treatment of primary aldosteronism.

- BP and serum K: htn and hypokalemia
  - PRA
    - if > 1.0, primary aldosteronism is unlikely
    - if < 1.0, ensure pt adequately salt and K loaded
  - 24h urine for K and aldo: if not elevated, check urine cortisol and DOC
    - if elevated urine K and aldo, adrenal CT
      - ◆ adenoma: adrenalectomy
      - ◆ equivocal/normal: postural stim test, plasma 18-OHB, bilateral adrenal vein sampling to lateralize
        - ◆ medication if not lateralized, otherwise adrenalectomy

### What is the biochemical hallmark of hyperaldosteronism?

- elevated plasma or urinary aldosterone indexed against urinary sodium excretion after sodium loading in combination w/ low PRA during sodium depletion

### What screening tests are available to look for aldosteronism?

- PRA
- 24h urine aldosterone
- aldo-to-renin ratio: not useful?
- postural stimulation test
- aldo levels w/ sodium loading
- cortisol metabolites: 18-OHcortisol, 18-oxocortisol

### What is the mechanism of action for the postural stimulation test, and how is it performed?

- stimulation of renin and increased aldo occur during upright posture → absent if autonomous aldo production
- plasma cortisol and aldo levels at 8am and again 2-4hrs later
  - aldo decreases in pts w/ primary aldosteronism w/ autonomous aldo production or GRA
  - increases in pts w/ idiopathic hyperaldosteronism or AII-R adenoma

### What is the mechanism of action for sodium loading testing?

- volume expansion in normal pts should decrease PRA, decrease aldo
- primary aldosteronism: renin secretion suppressed already, volume expansion doesn't change PRA or aldo

### What is the best test for localizing aldo production?

- adrenal vein sampling of aldosterone
  - high aldo concentration in adrenal w/ APA, contralateral suppression from normal gland
  - difficult to sample small R adrenal vein
  - do if bilateral disease and presentation classic for adenoma
  - do if solitary tumour in older pts

### What is the smallest APA that can be delineated w/ CT?

- 1cm → difficult to see w/ MR

### What factors can cause a false-negative diagnosis for hyperaldosteronism?

- potassium deficit: will blunt secretion of aldo → K and Na load pts
- beta-blockers and other antihypertensives: decrease PRA → d/c for 2 weeks prior to evaluation
- spironolactone: d/c 1mo prior

### What is the medical therapy for aldosteronism?

- bilateral hyperplasia: spironolactone (competitive antagonist of aldosterone R)
- amiloride
- CCB: decrease BP and aldo secretion
- ACEi

## Chapter 101 Questions - Adrenal.doc

### What are the secretory products of a pheochromocytoma?

- epi, NE
- dopa, dopamine
- peptides from APUD (amine precursor and uptake and decarboxylation) cells: ACTH, somatostatin, serotonin, enkephalin, calcitonin, VIP, neuropeptide, lipotropin, beta-endorphin, dynorphin

### What are the three common patterns of htn seen in pheo?

- sustained htn
  - little fluctuation, seen in MEN2
- paroxysmal htn
  - more common in F
- sustained htn w/ superimposed paroxysms

### What sx are present in pts w/ pheo?

- Symptoms
  - Sx due to catechols or htn: headache, sweating, palpitations, tachycardia, anxiety
  - tremulousness
  - chest pain
  - N/V
  - weakness, fatigue
  - wt loss
  - dyspnea
  - visual changes
  - dizzy/faint
  - constipation
  - seizure
  - catecholamine induced cardiomyopathy: CHF, MI, stroke, renal failure
  - shock
- Signs
  - BP changes
  - hyperhidrosis
  - increased/decreased HR
  - pallor
  - anxious
  - hypertensive retinopathy
  - dilated pupils
  - underweight
  - tremor
  - Raynaud's
  - fever
  - mass lesion: tumour in abdo or neck

### How often do attacks of htn occur in pts w/ pheo?

- > 1/wk in 75%, last <1hr in 80%

### What precursors may elicit an attack w/ pheo?

- none
- massage
- exercise
- certain posture
- trauma
- tight clothing
- straining or Valsalva
- bladder distension or voiding
- laugh, cough, sneeze, retch
- foods: tyramine (beer, wine, cheese)
- drugs: tyramine, histamine, methacholine, succinylcholine, phenothiazine, ACTH, beta-blockers

### What % of pts w/ pheo have normal BP?

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- 10%

### What is the mechanism of catecholamine induced cardiomyopathy?

- foci of myocardial necrosis, w/ inflammation and necrosis
- decreased BP due to global reduction in myocardial pump function, down-regulation of beta R, decreased in available myofibrils

### What % of pheo are sporadic vs. familial?

- 95% sporadic, 5% familial (may actually be 30%: ret oncogene)

What are the rules of 10's for pheo?

- 10% malignant, 10% multiple, 10% extra-adrenal, 10% have normal BP

### What familial disorders are associated w/ pheochromocytomas?

- MEN IIa (Sipple's syndrome): medullary carcinoma of thyroid, hyperparathyroidism, and pheo
- MEN IIb/III: MCT, mucosal neuroma, intestinal ganglioneuroma, Marfanoid, pheo
- neurofibromatosis: pheo in 1-2%
- VHL: if pheo present, classified as VHL type 2 (type 2a if RCC, 2b if no RCC)
- tuberous sclerosis
- Sturge-Weber → neurocutaneous disorder associated w/ infants: hemangioma, etc.

### How does pheo manifest in children differently vs. adults?

- h/a, N/V, wt loss, visual changes more common in kids
- polydipsia, polyuria, convulsions in 25% (rare in adults)
- puffy, red, cyanotic hands in 11%
- sustained htn in 90%, paroxysmal htn in <10%
- higher bilaterality (25%) and multiplicity (15-30%)
- higher incidence of malignancy

### How does one diagnose pheo?

- Labs
  - urinary catecholamines, metanephrines, and VMA
  - plasma NE, epi, dopamine, metanephrins (best test)
- Radiology
  - CT/MRI
  - MIBG scan if high index of suspicion → isotope picked up by tumour
  - echo, radionuclide scans

### What medications can increase or decrease serum catecholamines and urinary metabolites?

- Increase (interfere w/ fluorescence assays)
  - catechols: drugs containing catecholamines, L-dopa, tetracycline, erythromycin, CPZ, fluorescent substances (quinine, quinidine, bile in urine), clonidine w/d, EtOH
  - metanephrines: drugs containing catecholamines, MAOIs, benzos, rapid clonidine w/d, EtOH
  - VMA: drugs containing catecholamines, L-dopa, nalidixic acid, rapid clonidine w/d
- Decrease
  - catechols: fenfluramine
  - metanephrines: Renografin, fenfluramine
  - VMA: clofibrate, disulfiram, EtOH, MAOIs, fenfluramine (large doses)

### How does pheo appear on MRI?

- characteristically bright "light bulb" image on T2

### What is the only contraindication to surgery in pts w/ pheo?

- late pregnancy
  - treat w/ alpha blocker phenoxybenzamine until fetus mature, then do C-section w/ tumour excision

### How is BP controlled during OR?

- phenoxybenzamine (Dibenzylamine): long-acting alpha blocker
  - 20-30mg PO OD, increased by 10mg daily until BP stable and mild postural hypotension (usually 40-100mg daily)
  - prazosin is not used: reversible, can be overwhelmed by catecholamine surge
- phentolamine 1-5mg boluses, or as continuous infusion

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- beta blockers: only after alpha blockade completed, as may cause rise in total peripheral resistance due to unopposed alpha activity, esp if arrhythmia
- **volume: to avoid postural hypotension**
- metyrosine 0.5-1g PO TID-QID (tyrosine hydroxylase inhibitor): decreases rate of catechol synthesis
  - s/e: crystalluria, sedation, diarrhea, anxiety, psychic disturbance, extrapyramidal signs
  - reserve for pts w/ cardiomyopathy, multiple catechol-secreting paragangliomas, or resistance to  $\alpha$ -blockers
- CCB

### What meds should be avoided in pts w/ pheo?

- halothane
- propofol
- ketamine
- droperidol
- morphine
- cocaine
- tubocurarine
- atracurium
- pancuronium
- ephedrine
- CPZ
- metoclopramide

### What anaesthetic should be used in pts w/ pheo?

- thiopental followed by isoflurane

### What are the possible approaches to adrenalectomy and their indications?

- posterior: for bilateral or unilateral small tumours
- modified posterior: pt tilted slightly up, like Gil-Vernet dorsal lumbotomy
  - advantage: adrenal vein identified easily
- flank: standard
- thoracoabdominal: for large adenomas, large carcinomas, well-localized pheo (esp on R side)
- transabdominal: for pediatric patients → Chevron

### Describe the flank approach to the adrenal.

- extrapleural extraperitoneal 11<sup>th</sup> rib resection
- lumbocostal arch is used as a landmark
- R: liver lifted off anterior adrenal
  - do not dissect adrenal off kidney: used for retraction
  - dissection from lateral to medial along posterior and diaphragmatic muscle
    - ligate/clip small multiple adrenal arteries
  - vein clipped/tied and divided
    - **if pheo, vein clipped prior to artery**
    - notify anesthetist when vein clipped, as BP may drop
- L: Gerota's swept medially and inferiorly
  - divide splenorenal ligament
  - spleen and pancreas lifted superiorly
  - dissect superiorly first, drawing kidney down
  - on L medially, phrenic branch of venous drainage clipped
  - medial dissection along crus of diaphragm and aorta to renal vein and adrenal vein

### What are the indications for partial adrenalectomy?

- pts w/ bilateral disease
- pts at risk of multiple adrenal tumours: VHL type 2

### What are the indications for lap adrenalectomy?

- small to moderate pheo
- functional adrenal tumours > 3cm that demonstrate growth on serial imaging
- tumours > 4-5cm

### What are the contraindications to LA?

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- Absolute
  - invasive adrenal ca requiring en bloc resection of kidney and perinephric fat, spleen, pancreas, diaphragm, LN
  - symptomatic adrenal masses in pregnant pts
  - pheochromocytomas that demonstrate malignant behaviour w/ multiple sites or mets to LN
- Relative
  - prior intra-abdominal surgery or trauma
  - ?morbid obesity – not usually a problem: push harder, use longer trochars
  - uncorrected coagulopathy
  - large pheo

### Describe the process of R transperitoneal laparoscopic adrenalectomy.

- Preop
  - correct metabolic abnormalities and htn
  - think of adrenal insufficiency if not feeling well after adrenalectomy: don't look right
- Foley, flank position, axillary roll, padding
- no tape
- 4 trocars: 1 for camera, 3 5mm ports
  - 2 placed 2 cm below costal margin at midaxillary and anterior axillary lines
  - 3<sup>rd</sup> port in MCL ½ way b/w costal margin and umbilicus
- triangular ligaments incised
- liver retractor
- mobilize liver and duodenum
- dissect along anterior IVC in a cephalad direction
- divide adrenal vein: 2-3 hemoclips on IVC side, 1-2 on adrenal side
  - look for large inferior adrenal artery: divide
- release inferior pedicle
- incise Gerota's at junction of upper pole of kidney and adrenal
- retrieve adrenal

### What are the advantages and disadvantages to retroperitoneal adrenalectomy?

- Advantages
  - fewer structures to mobilize
  - no adhesions
  - ? less postop ileus
  - limits postop fluid collections
- Disadvantages
  - smaller working space
  - need expensive balloon
  - fewer landmarks
  - difficult if prior retroperitoneal surgery

### What are the causes of secondary hypertension?

- mnemonic: AORTA
  - Aorta: coarctation of the aorta
  - OCP and other meds
    - steroids
  - Renal causes
    - Malignancy
    - AVM
    - Renin secreting tumours
    - Vascular htn: RAS
  - Thyroid: hyperthyroid
  - Adrenal
    - Cushing's
    - Conn's
    - SIADH
    - Pheo
    - PAH (primary adrenal hyperplasia)
    - adrenal adenoma
    - adrenal carcinoma

### **Chapter 101 Questions - Adrenal.doc**

- glucocorticoid-remediable aldosteronism (GRA, or FHI)
- familial primary aldosteronism (FHII)





## **Chapter 105**

### **• Genitourinary Trauma •**

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#### **What are the most common causes of renal trauma?**

- Blunt
  - MVA
  - falls
  - assaults
- Penetrating
  - gunshot: 4% of all renal trauma
  - stabbing: usually from assaults or self-inflicted injury

#### **What is the most important determinant of injury in blunt renal trauma?**

- extent of deceleration
  - causes vascular damage: RA thrombosis, RV disruption, pedicle avulsion

#### **What is the best indicator of traumatic urinary system injury?**

- hematuria: micro or gross
  - degree of hematuria does not correlate w/ extent of injury → 36% of all renal vascular injuries have no hematuria

#### **How can one classify renal injury?**

- American Association for the Surgery of Trauma: Organ Injury Severity Scale for the Kidney (1989)
  - Grade I
    - contusion: micro/gross hematuria, GU studies normal
    - hematoma: subcapsular, nonexpanding w/o parenchymal laceration
  - Grade II
    - hematoma: nonexpanding perirenal hematoma confined to retroperitoneum
    - laceration: <1cm w/o urine extravasation
  - Grade III
    - laceration: >1cm depth w/o collecting system rupture or urine extravasation
  - Grade IV
    - laceration: laceration into collecting system
    - vascular: RA or RV injury w/ contained hemorrhage
  - Grade V
    - laceration: shattered kidney
    - vascular: avulsion of renal hilum, devascularizing the kidney

#### **What is a significant level of hematuria in trauma?**

- >5 RBC / HPF

#### **What are the indications for renal imaging?**

- Blunt trauma
  - gross hematuria
  - microscopic hematuria and:
    - shock (sBP < 90mmHg)
    - any hematuria in children
    - rapid deceleration mechanism
- Penetrating trauma
  - all cases

#### **What findings on CT suggest major renal injury?**

- medial hematoma: suggests vascular injury
- medial urinary extravasation: suggests collecting system injury



## Chapter 105 Questions - GU Trauma.doc

- lack of contrast enhancement

### What are the options for renal imaging in trauma?

- contrast-enhanced CT
  - do delayed scan to image entire collecting system (10min later)
- single-shot intra-operative IVP
  - indicated if find **unexpected retroperitoneal hematoma intra-operatively**
  - 2mL/kg of contrast, explore if not normal
- arteriography
  - define arterial injuries seen on CT
- US
  - confirms presence of 2 kidneys
  - defines retroperitoneal hematomas

### How can one manage renal trauma non-operatively?

- 98% of renal injuries can be managed nonoperatively → significant injuries only in 5.4% of renal trauma cases
- penetrating injuries can be managed nonoperatively if staged w/ CT
  - admit to hospital
  - bedrest
  - ambulate only if no gross hematuria
  - close F/U

### What are the indications for renal exploration after trauma?

- Absolute
  - persistent bleeding
  - expanding perirenal hematoma
  - pulsatile perirenal hematoma
- Relative
  - urinary extravasation
  - nonviable tissue
    - if > 20% nonviable tissue w/ parenchymal laceration + urinoma, increased complications
  - delayed diagnosis of arterial injury
  - segmental arterial injury
  - incomplete staging

### Describe the approach to renal exploration for trauma.

- transabdominal approach
  - complete inspection of intra-abdominal organs and bowel
- renal vessels isolated before renal exploration → **early vascular control decreases nephrectomy rate**
  - transverse colon lifted superiorly
  - small bowel lifted superiorly and to R
  - retroperitoneal incision medial and superior to IMV (almost directly anterior to aorta)
  - incision extended superiorly to ligament of Treitz
  - expose anterior surface of aorta and followed to L renal vein, apply vessel loop
  - R renal vein can be controlled through this incision as well
    - if not, Kocherize duodenum
- kidney exposed through peritoneum lateral to colon
- mobilize off Gerota's fascia
- release of splenic or hepatic flexure
- Gerota's opened and injured kidney dissected out
- renal reconstruction
  - complete renal exposure
  - debride nonviable tissue
  - hemostasis by ligating bleeding vessels w/ 4-0 chromic
  - watertight closure of collecting system w/ 3-0 absorbable suture
  - coverage or approximation of renal defect – use Gelfoam
  - partial nephrectomy needed if polar injury cannot be reconstructed
    - open parenchyma covered w/ pedicle flap of omentum
- renovascular injury repair
  - repair w/ 5-0 Prolene

## Chapter 105 Questions - GU Trauma.doc

- repair often not possible in renal artery thrombosis → time constraints necessitate nephrectomy
- segmental venous injury: ligate vessel
- place drains

### What is the pathogenesis of renal artery thrombosis from blunt trauma?

- mobility of kidney causes stretch of artery
- intima is low in elastic fibers: disrupts
- thrombus occludes the vessel, causing ischaemia → nonrecoverable beyond ~8 hrs

### What are the indications for nephrectomy in trauma?

- unstable patient w/ low temp and poor coagulation → pack bed and return in 24h
- extensive renal injuries when pts life threatened

### What are the complications from renal trauma?

- persistent urinary extravasation → treat w/ stent
  - urinoma
  - perinephric infection
  - renal loss
- delayed hemorrhage: can occur several weeks out
  - treat w/ bedrest and hydration, angio/embolization if persists
- perinephric abscess
  - tx w/ perc drainage
- hypertension

### What are the mechanisms for arterial hypertension after renal trauma?

- renal vascular injury w/ stenosis/occlusion of main renal artery
- compression of the renal parenchyma w/ blood or urine
- post-traumatic AV fistula

### What are the etiologies of ureteral trauma?

- External trauma: rare (<4% and 1% of penetrating/blunt traumas)
  - GSW: microvascular damage seen 2cm above and below pt of transection → debride back to a bleeding edge
  - UPJ disruption rare: dx w/ delayed CT
- Open surgical injury
  - etiology: TAH (54%), colorectal surgery (14%), pelvic surgery (8%), abdominal vascular surgery (6%)
- Laparoscopic injury
  - etiology: lysis of endometrial adhesions, endometrial involvement of ureter, intraperitoneal adhesions
- Ureteroscopic injury
  - persistence of stone basketing after ureteral tear
  - previously irradiated tissue

### What are the RF for ureteral injury in pts undergoing abdominal vascular surgery?

- reoperation
- placement of vascular graft anterior to the ureter
- large dilated arterial aneurysms → retroperitoneal inflammation

### How can one diagnose ureteral injury?

- Intraoperative recognition
  - inject methylene blue 1-2mL
- Post-op recognition
  - hematuria: absent in 25-45% of injuries
  - fever, increased WBC, local peritonitis
- Imaging
  - IVP: intraop one-shot
  - CT: absence of ureter on delayed images (5-20 min)
  - retrograde ureterography
  - antegrade ureterography

### What is the treatment of ureteral injury?

- External injury

## Chapter 105 Questions - GU Trauma.doc

- contusion: may heal w/ stricture
  - stent placement: if minor contusion → excise if in doubt
  - direct u-u
    - ◆ large areas of contusion treated w/ excision and ureteroureterostomy
    - ◆ 90% success in upper 2/3 of ureter
    - ◆ place stent
  - staged repair or nephrectomy if pts w/ severe shock, uncontrollable bleeding, severe bowel injury
    - ◆ tie off damaged ureter w/ long silk, drain kidney percutaneously (post-op)
- upper ureteral injury
  - direct u-u
  - transureteroureterostomy
  - ureterocalycostomy
  - autotransplantation
  - ileal interposition segment: only for delayed repair
- midureteral injury
  - direct u-u
  - trans u-u → used when direct u-u or bladder flap/hitch not possible (severe bladder scarring, congenitally small bladder, very long segment of missing ureter)
    - ◆ contraindicated w/ hx TCC
- lower ureteral injury
  - ureteric reimplantation
  - psoas hitch: better than u-u in lower 1/3, as ureter has tenuous blood supply
  - Boari flap: may take too long in the injured pt
- partial transection: direct repair
- Surgical injury
  - ligation: remove clip/ligature and observe, place stent
  - transection
    - immediate recognition → controversial if graft present
      - ◆ nephrectomy vs. u-u → can repair, and perform nephrectomy if leaks postop
    - delayed recognition
      - ◆ attempt stent placement
      - ◆ place NT if stent fails, reattempt stent 2/52 later
      - ◆ wait several months and perform open repair in pts w/ persistent leaks or ureteral stricture
- Ureteroscopic injury
  - avulsion: as previous
  - perforation: stent

### What are the principles that must be followed in ureteroureterostomy?

- mobilize ureter carefully w/ sparing of adventitia
- debride ureter liberally until edges bleed
- repair under magnification
- spatulate edges
- tension free watertight anastomosis
- place stent and retroperitoneal drains
- omental interposition to isolate repair

### What are the indications for nephrectomy after ureteral injury?

- severe associated visceral injuries or severe ipsilateral renal injury when renal repair not possible
- poor renal function
- severe pan ureteral injury
- persistent ureteral fistula

### What are the causes of bladder injury?

- Blunt
  - MVAs
    - 85-100% have associated pelvic #
      - ◆ pelvic # less common in kids: bladder rides above pelvis when full
    - 10-15% of all pelvic # have bladder +/- urethral injury
- Penetrating
- Iatrogenic

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→ during surgery

### Describe the algorithm for pts w/ pelvic # and suspected GU injury.

- Blood at meatus?
  - no: pass Foley
    - hematuria absent: observe
    - hematuria present:
      - ◆ cystogram > 300cc contrast
        - ◆ extravasation: intraperitoneal (OR) vs. extraperitoneal (Foley drainage)
      - ◆ CT/IVP if suspect renal trauma
  - yes: RUG
    - urethral injury: surgical intervention

### What are the sx of bladder injury?

- hematuria
  - present in 99% of bladder rupture
- blunt trauma: lower abdo pain, tenderness, bruising
- urethral catheter doesn't drain
- delayed dx: fever, absence of voiding, peritonitis, increased BUN/Cr
- shock

### What imaging is used to detect bladder injury?

- cystography
  - 100% accurate in diagnosing significant bladder injury
  - 350cc of 30% contrast by gravity
  - need post-drainage film
- CT cystogram
  - need to dilute contrast: undilute contrast is so dense that CT quality is compromised
  - must fill in retrograde fashion
- static cystogram → not recommended
  - clamp Foley after IV contrast

### How can one classify bladder injuries?

- Contusions = trauma pt w/ hematuria w/ no evidence of urethral or renal injury and normal cystogram
  - no tx required
- Extraperitoneal: 65%
  - due to direct laceration from bony fragment
  - manage w/ catheter drainage only
- Intraperitoneal: 25%
  - usually due to high pressure burst at dome
- Combined extraperitoneal and intraperitoneal: 10%

### What are the contraindications to conservative management w/ extraperitoneal bladder rupture?

- bone fragment projecting into bladder
- open pelvic fracture
  - open plating of symphysis
- rectal perforation
- pts undergoing laparotomy for other reasons
- BN injury

### Why should an extraperitoneal bladder rupture be repaired if the pt is to undergo open plating of the pubis symphysis?

- pt undergoing open operation already
- formal bladder repair thought to decrease potential complications by 50%
- can place large SP tube
- stops urine from infecting hardware
- prevents suction drains from drawing urine out of bladder

### What are the reasons that intraperitoneal bladder ruptures should be repaired primarily?

- unlikely to heal spontaneously: usually larger than suggested by cystogram

## Chapter 105 Questions - GU Trauma.doc

- associated w/ persistent urinary leakage
- peritonitis from urine

### How does one manage bladder injuries postoperatively?

- extraperitoneal: antibiotics on day of injury until 3d after Foley removed
- intraperitoneal: antibiotics perioperatively only, and again when Foley removed
- cystogram at 14d (7d if bladder repaired), repeat at 21d if not healed

### How does one avoid entering the pelvic hematomas that usually coexist in pts undergoing open repair of extraperitoneal rupture?

- stay midline
- close bladder in 2 layers

### What are the etiologies of urethral injury?

- Posterior
  - pelvic #: urethral injury in 4-14%
  - shear injury: due to blunt trauma → stretches at membranous urethra
    - may be due to bony fragments
- Anterior
  - straddle injury
  - direct injury to penis: penetrating
  - gunshot

### How can one diagnose a urethral injury?

- Hx/Px
  - pelvic fracture
  - blood at urethral meatus (present in 50% of significant urethral injuries)
  - inability to void
  - inability to pass catheter
  - palpably full bladder
  - scrotal or perineal hematoma or swelling
  - "high-riding" prostate → unreliable
  - anterior injury: large hematoma or swelling from urinoma
- Imaging
  - RUG

### Describe the technique of RUG.

- place 14F Foley into fossa navicularis, place 1-2cc into balloon
- place pt on 30° wedge
- instill 10cc of 30% contrast and take pics: fluoro or static Xrays

### How can one classify urethral injuries?

- Colapinto classification (J Urol 1977)
  - Type I: urethral stretch injuries
  - Type II: membranous urethral disruption proximal to GU diaphragm
  - Type III: membranous urethral disruption both proximal and distal to GU diaphragm
- partial vs. complete disruption
  - partial: contrast extravasates + contrast seen in bladder

### Describe the management of the posterior urethral injury.

- Initial management
  - ensure pt stable: ABCs
  - primary realignment
    - open primary realignment: ++ ED, incontinence, stricture formation, and blood loss → not recommended
    - placement of catheter across defect: mild stricture in 50-65%
      - ◆ gentle placement of 16F Silastic by urologist once
      - ◆ if fails, try endoscopic realignment
      - ◆ if pt going to OR, open bladder and inspect bladder for rupture
        - ◆ attempt antegrade cystoscopy or combined antegrade/retrograde
        - ◆ **Davis interlocking sounds: do not use → high rate of associated injury**

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- ◆ place SP tube after success
- ◆ if fails, place SP tube only
- leave Foley x 6 weeks, get RUG and VCUG
- leave SP tube in for 2 weeks → emergency outlet if rapid stricture development
- SP tube
  - 96% urethral stricture
  - use if pt unstable
  - if anterior pubic hardware, place high in bladder as possible and tunnel under skin to prevent plate infection
- Delayed reconstruction
  - wait 3/12 for urethral reconstruction
  - Preop evaluation
    - imaging to delineate stricture: RUG + VCUG, MRI also used
    - assess BN: should be closed at rest, and open during voiding
  - Endoscopic reconstruction
    - VIU for short urethral strictures
    - open posterior urethroplasty for significant urethral distraction injuries
    - cut-to-light procedures: unacceptable failure and complication rates
  - Surgical reconstruction
    - Perineal
      - ◆ excise scar tissue and anastomose bulbar urethra to prostatic urethra
      - ◆ female pts: endoscopic core-through procedure if short
        - ◆ distal strictures: hypospadiac opening into anterior vagina
        - ◆ complete disruption: bladder flap neourethral reconstruction
    - Pubectomy
      - ◆ may be required in severe injuries w/ very long distraction or marked displacement of prostate
    - Staged procedure

### What are the indications for pubectomy in posterior urethral reconstruction?

- to remove urethrocutaneous fistulae and large urethral diverticulae
- to maximize exposure, scar removal, and reconstruction w/ tension-free anastomosis in long strictures

### What are the indications for a staged urethroplasty for urethral strictures?

- extensive stricture (w/o available penile skin for flap)
- previous failed anastomotic urethroplasty
- severe perineal infection/inflammation

### What are the complications of posterior urethral reconstruction?

- ED: 13-30% of pts w/ pelvic # and urethral injury
  - etiology: injury to parasympathetic nerves during injury, arterial insufficiency, anejaculation due to BN scarring
- incontinence: 2-4% overall (50% if open BN prior to urethroplasty)
  - treat w/ pseudoephedrine or AUS
- areflexic bladder: CIC
- stricture: 12-15% stricture recurrence rate

### Describe the management of the anterior urethral injury.

- Initial management
  - catheter realignment: worse stricture rate
  - primary surgical repair: for GSWs
    - caution when debride corpus spongiosum after trauma → bruised tissue may mimic necrotic tissue
  - SP tube: best for crush injuries or straddle injuries
- Delayed reconstruction
  - plan for 3 months post-injury
  - RUG + VCUG preop
  - excise scar w/ anterior urethroplasty

### What are the complications from anterior urethral repair?

- ED
- stricture: <5% after anterior urethroplasty

### What is the most common cause of penile amputation?

## Chapter 105 Questions - GU Trauma.doc

- self-inflicted: psychosis

### What are the indications for penile replantation?

- attempt to reattach against pts wishes → pts usually psychotic w/ poor control
- exception: nonpsychotic transsexual pts, esp if living as women and taking hormones under psychiatric care for > 1yr

### What are the options for penile lengthening after traumatic amputation?

- release suspensory ligament
- defatting pubis to facilitate longer protruding penile length
- place rigid prosthesis after multiple relaxing incisions in cavernosa to telescope penis

### What principles should be followed in penile replantation after traumatic amputation?

- wrap penis in sterile gauze w/ sterile NS  
→ penis unlikely to survive > 24h cold ischemia
- 2-layer closure over catheter
- minimal dissection along NVB
- close tunica albuginea w/ 4-0 absorbable
- repair dorsal artery w/ 11-0 nylon
- repair dorsal vein w/ 9-0 nylon
- repair dorsal nerve w/ 10-0 nylon
- SP tube placement
- do not attempt repair of cavernosal arteries

### What is the management of the GSW to the penis?

- primary repair for most low-velocity injuries  
→ irrigate and close primarily if no deep structures involved  
→ repair corporal injuries by approximating tunical margins w/ buried nonabsorbable or absorbable sutures  
→ close urethral injury w/ watertight, spatulated catheter stented technique  
→ posterior injury: ? staged procedure
- staged treatment for massive injury: shotgun blast

### What is the etiology of penile fracture?

- striking of erect penis against symphysis during intercourse after penis slipped out of vagina
- manual bending during masturbation
- blunt trauma to erect penis

### How can one diagnose penile fracture?

- Hx/Px  
→ blow to penis w/ "popping" sound, w/ pain and immediate detumescence  
→ penile swelling  
→ ecchymosis  
→ palpable corporal defect  
→ "rolling sign": clot lying near fracture palpable as firm immobile swelling over which penile skin can be rolled  
→ "eggplant" deformity  
→ "butterfly" sign: blood extravasation around Colles' fascia
- Imaging  
→ US: not always helpful  
→ MRI: probably unnecessary → can localize exact injury, preventing need for complete penile degloving  
→ cavernosography: use only if dx in doubt  
➤ place 25G butterfly needle into cavernosum, instill 30% contrast → delayed images x 10min

### Describe the management of penile fracture.

- Surgical  
→ immediate repair w/ evacuation of hematoma, inspection of tunical laceration, and repair  
→ absorbable sutures for cavernosal repair  
→ no penile compression dressing after repair, can use adherent polyurethane film to prevent further swelling  
→ repair associated urethral injuries
- Nonoperative  
→ sedatives, ice packs, pressure bandages: poor outcomes

## Chapter 105 Questions - GU Trauma.doc

- deformity in 10% and prolonged penile pain

### Describe the management of penile soft tissue injury.

- irrigation, debridement, and antibiotics
- dog bites: Ancef
- human bites: ampicillin/sulbactam → broader coverage for *Eikenella corrodens*
- tetanus shots
- tests for: HIV, hepatitis, TB, syphilis, HSV

### How can one deal with a patient w/ the penis caught in a zipper?

- local anaesthetic block
- lube zipper w/ mineral oil
- attempt x 1 to open zipper
- cut zipper slider
- pull apart zipper teeth w/ snaps

### What are the etiologies of trauma to the testis?

- Blunt trauma
  - assaults
  - sports injuries
  - MVA
  - self-inflicted
- Penetrating
  - GSW

### What are the associated injuries seen w/ testis trauma?

- injury to surrounding structures: thigh, penis, perineum, urethra
- bowel injury: if hernia
- transection of the vas

### Describe the management of the injured testicle.

- Imaging
  - US
  - radionuclide scans: not indicated for trauma
- Surgical repair
  - explore and repair all significant hematocele, intratesticular hematoma, or testicular rupture
    - even small tears can gradually extrude tubules
  - explore through midline incision, conserve as much testicular tissue as possible, copious irrigation
  - remove scrotal hematoma
- Nonoperative repair
  - higher orchiectomy rates, longer hospital stays
  - used only if insignificant injury
    - 40% infection/necrosis requiring orchiectomy if intratesticular hematoma not treated

### What are the etiologies of genital skin loss?

- penetrating injury
- infection: Fournier's → iatrogenic
- burns
- constricting bands → used for prolonging erection
- traction from mechanical devices (ex: farm or industrial machinery) or vacuums

### Describe the management of penile skin loss.

- NS gauze
- skin graft and local flaps
  - avoid using avulsed skin: often becomes necrotic
  - STSG from anterior thigh
- donor site care
  - control bleeding by epi-soaked Telfa dressing
  - 1% silver sulfadiazine cream, 3% bismuth gauze, Jelonet



## **Chapter 105 Questions - GU Trauma.doc**

- place large semiocclusive dressing
  - don't use vapor-occlusive dressings: high rate of infection
- remove dressing when lifts off spontaneously or if infection occurs
- post-op wound management
  - bulky gauze dressing soaked in mineral oil
  - held in place by 4-0 silk sutures
  - IV Ancef x 5d
  - avoid sex x 6 weeks

### **Describe the management of scrotal skin loss.**

- partial
  - close acutely if < 50%
  - > 50%: place testes in thigh pouches or treat w/ wet dressings until reconstruction
  - local skin flaps: medial thigh, rectus, buttock, anterolateral thigh
- total
  - STSG meshed
  - thigh flaps

### **What is the cause of hemodynamic instability in pelvic #?**

- venous: 90%
- arterial: 10%

### **What are the indications for acute pelvic ex-fix?**

- persistent shock despite resuscitation
- high risk pelvic #: APC +/- VS, not LC

### **What are the indications for pelvic angiography?**

- persistent shock despite tx
- unexplained shock: low risk pelvic #



## **Chapter 106**

### **• Use of Intestinal Segments and Urinary Diversion •**

---

**What is the blood supply for a pedicle of stomach brought down to the pelvis?**

- gastroepiploic vessels: L or R
  - pedicle may be entire antrum or wedge of fundus

**How does the anatomy of the ileal mesentery differ from the jejunal mesentery?**

- ileum
  - smaller diameter
  - multiple arterial arcades
  - vessels are smaller
  - thicker mesentery
- jejunum
  - larger diameter
  - single arterial arcades
  - larger diameter vessels
  - thinner mesentery

**What portions of the small bowel tend to lie within the pelvis?**

- often are exposed to radiation during pelvic rads
  - last 2 inches of terminal ileum
  - 5 feet of small bowel beginning 6 feet from ligament of Treitz

**What are the weak points involving vascular supply to the colon?**

- Sudeck's critical point
  - b/w junction of the sigmoid and superior hemorrhoidal arteries
- midpoint b/w middle colic and R colic arteries
- midpoint b/w middle colic and L colic arteries

**What are the advantages and disadvantages of stomach over other intestinal segments for urinary diversion?**

- Advantages
  - less permeable to urinary solutes
  - acidifies urine
  - net excretion of chloride and protons
  - produces less mucus
  - useful in pts w/ decreased amount of intestine, and use of more would cause nutritional problems
- Disadvantages
  - hypochloremic metabolic alkalosis
  - antral exclusion causes elevated circulating gastrin levels → causes ulcers
  - hematuria-dysuria syndrome

**What are the complications from use of stomach in diversion?**

- Early
  - gastric retention from stomach atony
  - hemorrhage
  - hiccups
  - pancreatitis
  - duodenal leak
- Late
  - dumping syndrome
  - steatorrhea
  - small stomach syndrome
  - increased intestinal transit time

## Chapter 106 Questions - Urinary diversion.doc

- bilious vomiting
- afferent loop syndrome
- hypoproteinemia
- Fe deficiency anemia
- bowel obstruction

### What complications result from loss of significant portions of ileum?

- nutritional problems from lack of vitamin B12 absorption
- diarrhea from lack of bile salt reabsorption
- fat malabsorption

### What are the problems associated w/ operating on unprepared bowel?

- increased wound infection rate
- increased intraperitoneal abscesses
- increased anastomotic dehiscences

### What are the contraindications for whole-gut irrigation bowel preparation?

- unstable cardiovascular system
- cirrhosis
- severe renal disease
- CHF
- obstructed bowel

### What are the doses for mechanical bowel preparation?

- Conventional
  - CF started 2d pre-op
  - 45mL Fleet PhosphoSoda 2d pre-op, 30mL 1d pre-op
- Whole-gut irrigation
  - CF started 1d pre-op
  - 2-4L GoLYTELY 1d pre-op

### What are the advantages and disadvantages of using antibiotic bowel preparations?

- Advantages
  - decreases post-op complications
  - decreases wound infections
- Disadvantages
  - increase in incidence of diarrhea
  - pseudomembranous colitis: abdo pain, diarrhea w/o fever or chills
    - pts can develop toxic megacolon → mortality 15-20%
    - *C. difficile* in majority of cases
    - treat w/ PO vanco or metronidazole, d/c other antibiotics
  - theoretical increased incidence of tumour implantation
  - monilial overgrowth: thrush, stomatitis, diarrhea
  - malabsorption

### What are the various regimens of antibiotic bowel preparation?

- kanamycin 1g PO q1h x 4, then QID x 3d preop → "single best agent"
- erythromycin base 1g + neomycin 1g PO at 1pm, 2pm, 11pm x 1d preop
- neomycin 1g + metronidazole 750mg PO QID x 2d preop

### What are the principles of surgical technique for intestinal anastomoses?

- adequate exposure
  - wall off area of anast to prevent spillage
- maintain good blood supply to the severed ends of the bowel
  - prevent tension, excessive dissection, excessive cautery, tying sutures too tight
- prevent local spillage
  - ensure bowel prepped
- serosa to serosa apposition
  - watertight and w/o tension, inverted suture line
- don't strangulate sutures when tying

## Chapter 106 Questions - Urinary diversion.doc

- realignment of the mesentery

### What are the advantages of a stapled anastomosis?

- better blood supply to healing margin
- reduced tissue manipulation
- minimal edema w/ uniformity of suture placement
- wider lumen
- easier
- decreased time
- decreased paralytic ileus

### Why do we give pts H<sub>2</sub> blockers after bowel surgery?

- keeps gastric pH > 5 during period of ileus
- reduces incidence of gastric stress ulceration

### What are the complications of intestinal anastomoses?

- leakage of fecal contents
- Fistulae
  - generally occur weeks after OR
    - fecal: 4-5%
    - urinary
- Infectious complications
  - sepsis
  - wound infection
  - wound dehiscence
  - pelvic abscesses
- bowel obstruction
  - due to adhesions, recurrence, volvulus, internal hernia, severe stenosis
- hemorrhage
  - usually due to failure to secure bleeding at time of anastomosis or to ulcers
- anastomotic stenosis
  - edema vs. ischaemia
- pseudo-obstruction of the colon (Ogilvie's)
  - rupture if > 12-15cm → needs cecostomy

### How can one reduce the incidence of post-op bowel obstruction?

- use nonirradiated bowel
- use well-vascularized bowel
- close apertures
- reperitonealize isolated segment
  - tack antimesenteric border to lateral abdominal wall peritoneum → prevents herniation into raw pelvis
- decompress GI tract post-op
- place omentum over anastomosis
- reconstitute pelvic floor after exenteration w/ mesh

### What are the complications of the isolated intestinal segment?

- intestinal stricture
  - due to lymphoid depletion of the segment exposed to urine
- elongation of the segment
  - distal obstruction if in ileal conduit
  - failure of CIC in continent diversions
  - may get volvulus

### What types of abdominal stomas can be created?

- nipple stoma: "rosebud"
- flush stoma
- loop end ileostomy
  - good for obese pts

### What are the complications of intestinal stomas?

## Chapter 106 Questions - Urinary diversion.doc

- parastomal skin lesions
- bowel necrosis
- bleeding
  - usually from varices → tx w/ transhepatic portal shunt
- dermatitis
- parastomal hernia: 5%
  - treatment reserved for pts that have failed conservative tx and are significantly symptomatic
    - high rate of recurrence, high morbidity of procedures
  - untreated hernias will usually worsen, and earlier repair may be easier
  - tx: suprafascial synthetic wrap to close hernia defect vs. stomal relocation
- prolapse
- obstruction
- stomal retraction
- stomal stenosis
  - less for loop stomas

### How can one classify parastomal skin lesions?

- irritative
  - hypopigmented, hyperpigmented, or skin atrophy
- erythematous erosive
  - macular, scaling, and loss of epidermis
- pseudoverrucous
  - wartlike

### How does a refluxing anastomosis affect the kidney?

- no evidence that VUR is detrimental after conduit/continent diversions
- upper tracts can be followed periodically w/ loopogram

### What are the important surgical principles when performing ureterointestinal anastomosis?

- mobilize minimal amount of ureter
- do not strip ureter of periadventitial tissue
- use fine absorbable sutures
- watertight mucosa-to-mucosa apposition
- bowel should be brought to ureter, not other way around
- fix bowel to abdominal cavity
- retroperitonealize anastomosis

### What are the causes of ureterointestinal stricture?

- ischemia
- urine leak
- radiation
- infection

### What are the various types of ureterocolonic anastomoses that can be performed?

- Leadbetter/Clarke
  - nonrefluxing, submucosal tunnel
  - implant under strip of taenia in midline w/ 5-0 PDS
- transcolonic technique of Goodwin
  - nonrefluxing submucosal tunnel created inside bowel w/ snap
  - anastomosis performed w/i the bowel
- Strickler
  - nonrefluxing submucosal 2cm tunnel created laterally w/ snap
  - serosal suture line in line w/ bowel, perpendicular to submucosal course of ureter
- Pagano
  - nonrefluxing submucosal tunnel
  - taenia incised for 4-5cm, mucosa separated from submucosa
  - button of mucosa removed, ureters spatulated and sutured to mucosa from outside
- Cordonnier and Nesbit techniques
  - no tunnel, refluxing anastomosis → like Bricker for colon
  - not desirable for ureterosigmoidostomies

## Chapter 106 Questions - Urinary diversion.doc

### What are the various types of small ureteroileal anastomoses that can be performed?

- Bricker
  - refluxing end-to-side anast
  - excise small button of bowel, spatulate ureter for 5mm, suture full thickness of ureter to full thickness of bowel w/ 5-0 PDS
- Wallace
  - end of intestine sutured to end of ureter → 3 types:
    - end of one ureter sutured to other, then sutured to bowel
    - Y-anastomosis b/w ureters, sutured to bowel
    - head-to-tail ureteroureteral anastomosis formed, sutured to bowel
  - all ureters spatulated for 1.5-2cm
  - **lowest complication rate for any ureteral intestinal anastomotic techniques**
- tunnelled small bowel anastomosis
  - non-refluxing anastomosis w/ submucosal tunnel
- split-nipple technique
  - ureter spatulated and turned back on itself, end of ureter secured to adventitia
- LeDuc
  - nonrefluxing anastomosis by laying ureter onto interior of bowel, eventually resulting in submucosal tunnel after it is reepithelialized
- hammock anastomosis
  - conjoining ureters and implanting them into small bowel in nonrefluxing manner
  - close intestinal wall over ureters

### What are the contraindications for the Wallace technique?

- extensive CIS
- high likelihood of recurrence in on ureter
  - tumour at anast would block both ureters

### What are the types of intestinal antireflux valves that can be created?

- ileocecal intussusception
  - strip 8cm of distal ileum, serosa scarified
  - segment intussuscepted into cecum, secured to cecal wall w/ 3-0 silk
  - significant chance for failure: often reduces
- ileoileal intussusception
- ileal nipple valve placed into colon
  - simplest type
  - mesentery cleared from last 8cm, distal 6cm scarified and turned back on itself
  - end of inverted ileum sutured w/ 4-0 PDS
  - incision on taenia made to accommodate the segment, serosa sutured to colon serosa

### What complications can occur from ureterointestinal anastomoses?

- leakage
- reflux
- fistulas: 3-9%
  - usually occur in 1<sup>st</sup> 7-10d
- strictures: more common in L ureter, found as ureter crosses over aorta
  - lowest incidence of stricture w/ Pagano technique w/ acceptable incidence of reflux
  - reimplant: 90% success, endoscopic tx: 70% success
  - metallic stents in pts w/ limited life expectancy
- pyelonephritis
  - 12% in conduits, 13% w/ antirefluxing colon conduits
- renal failure
  - pts w/ GFR > 40 ml/min tolerate a continent diversion
  - pts w/ Cr < 180 do well w/ intestine interposed in GU tract

### What are the indications and contraindications for a conduit?

- Indications
  - after cystectomy
  - due to a diseased bladder

## **Chapter 106 Questions - Urinary diversion.doc**

- before transplant in pt w/ bladder that cannot adequately receive ureters
- dysfunctional bladder that result in persistent bleeding, obstructed ureters, poor compliance, upper tract deterioration and inadequate storage w/ UI
- Contraindications
  - short bowel syndrome
  - IBD
  - extensive radiation

### **Describe the technique used to create an ileal conduit.**

- 10-15cm segment selected 10-15cm from ileocecal valve
- cecum mobilized
- ileal mesentery transilluminated and major arcade identified
  - mesentery penetrated
  - peritoneum incised overlying both sides of the mesentery
  - tissue clamped, severed, and tied w/ 4-0 silk
  - repeated at other side of segment
- isolated ileal segment placed caudad, ileoileostomy performed
  - close mesenteric window w/ 3-0 interrupted silk
- flush isolated segment w/ NS
- bring L ureter over great vessels, under sigmoid
- perform anast

### **What are the complications of ileal conduit (or any bowel segment)?**

- Early
  - urine leak
  - bowel leak
  - sepsis
  - pyelonephritis
  - wound infection
  - wound dehiscence
  - GI bleed
  - abscess
  - ileus
- Late
  - conduit bleed
  - bowel obstruction
  - ureteral obstruction
  - parastomal hernia
  - stomal stenosis
  - stone formation
  - excessive conduit length
  - hyperchloremic metabolic acidosis
  - conduit infarction
  - volvulus
  - conduit stenosis
  - conduit-enteric fistula
  - hypertension
  - CRF
  - death

### **What are the contraindications of jejunal conduit?**

- severe bowel nutritional disorders
- presence of another acceptable segment of bowel

### **What is the electrolyte disturbance that occurs w/ jejunal conduit?**

- hyperkalemic, hyponatremic, metabolic acidosis
  - tx: sodium chloride, thiazides to tx hyperkalemia

### **What types of colon conduits can be created?**

- transverse

## Chapter 106 Questions - Urinary diversion.doc

- use w/ want to be sure segment is not irradiated
- sigmoid
  - use in pts undergoing pelvic exenteration and colostomy → no bowel anastomosis needs to be made
- ileocecal

### What are the contraindications to a sigmoid conduit?

- disease of this segment
- ligated hypogastric arteries w/ rectum left in situ
- extensive pelvic radiation
- IBD
- chronic diarrhea

### What is the role of the ileal vesicostomy?

- used in pts w/ spinal cord disease
  - easier to care for an abdominal stoma

### How can one classify problems of inserting bowel into the GU system?

- metabolic
- neuromechanical: involve gut configuration, which affect storage and contraction of the bowel
- technical-surgical

### What are the metabolic complications of diversion?

- **mnemonic: G-DIVERSION**
- Growth retardation
  - fractures
- Drug metabolism abnormality
  - problem w/ drugs that are absorbed by GI tract, and excreted unchanged by kidney
    - Dilantin, certain antibiotics, chemo (MTX)
  - drain continent diversions w/ catheter during time drugs are given
- Infections
  - increased bacteriuria, bacteremia, and sepsis
  - pyelonephritis
  - tx only pts w/ *Proteus* or *Pseudomonas*
- Vitamin B<sub>12</sub> deficiency
- Electrolyte abnormalities
  - stomach: hypokalemic hypochloremic metabolic alkalosis
    - treat w/ PPI, or may need to redo w/ another segment
  - jejunum: hyponatremic hyperkalemic hypochloremic metabolic acidosis, azotemia
    - due to increased secretion of sodium and chloride w/ increased resorption of potassium and hydrogen ions
    - loss of sodium carries water, and pt dehydrates, w/ RAA stimulation
      - ◆ will worsen w/ TPN
    - treat w/ NS and NaHCO<sub>3</sub>
      - ◆ may treat hyperkalemia w/ potassium wasting diuretic (thiazide)
  - ileum/colon: hyperchloremic metabolic acidosis (plus hypokalemia w/ colon)
    - due to ammonium absorption in exchange for carbonic acid at Na-H antiport: secrete CO<sub>2</sub> and water, absorb H<sup>+</sup> and ammonium w/ chloride
    - treat w/ alkalizing agents or blockers of Cl<sup>-</sup> transport: **CPZ 25mg PO TID**
    - lose K more w/ colon, as it does not resorb K as much as ileum: tx w/ K-Na-citrate (PolyCitra K)
  - hypokalemia and total body depletion of K<sup>+</sup>
    - more common in ureterosigmoidostomy
    - usually due to renal potassium wasting from renal damage, osmotic diuresis, and loss through GI secretion
    - if associated w/ severe hyperchloremic metabolic acidosis, must replace K<sup>+</sup> and correct acidosis w/ bicarbonate
  - hypomagnesemia
    - seen w/ hypocalcemia
- Renal failure
- Stones
  - MAP (Mg ammonium phosphate) stones
  - RF: hyperchloremic metabolic acidosis, pre-existing pyelo, UTI w/ urea-splitting organism
- Impaired gut: problems from removing gut from GI tract
  - vitamin B<sub>12</sub> deficiency



## Chapter 106 Questions - Urinary diversion.doc

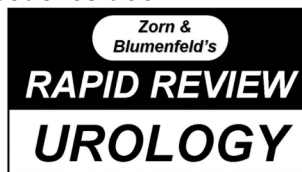
- malabsorption of bile salts, fat,  $\text{Ca}^{2+}$ , folic acid
  - bile salts saponify Ca, prevent complexing w/ oxalate, causing increased oxalate absorption
- anemia
- neurologic abnormalities
- loss of ileocecal valve: reflux of bacteria into ileum → overgrowth → nutritional abnormalities → interference w/ FA reabsorption → diarrhea
- loss of colon: diarrhea, loss of bicarb due to lack of reabsorption, dehydration
  - nocturnal BM, fecal incontinence
- Osteomalacia
  - occurs w/ mineralized bone reduced, and osteoid component of bone excessive
  - due to excess protons buffered by bone w/ release of bone calcium
    - occurs w/ persistent acidosis, vitamin D resistance, excessive Ca loss by kidney
  - sx: lethargy, joint pain, proximal myopathy
- Neoplasia: urothelial/intestinal cancer
  - adenoca, polyps, sarcoma, TCC
    - etiology not understood
  - may occur even w/ no urine: excise ureterointestinal anastomoses if defunctionalized
- Sensorium alterations
  - due to Mg deficiency, drug intoxication, abnormalities in ammonium metabolism, DM hyperglycemia
  - ammoniogenic coma → in pts w/ cirrhosis
    - tx: drain diversion, give neomycin to reduce ammonia load from GI tract, stop protein consumption, lactulose
    - arginine glutamate 50 in 1L of D5W: complexes w/ ammonia, allows for formation of glutamine in the liver
  - altered hepatic metabolism
    - liver adapts to increased solute load by increasing its capacity for ureagenesis

### What factors influence the amount of solute and absorption into bowel from urine in diversions?

- segment of bowel used
- surface area of bowel
- amount of time urine exposed to the bowel
- concentration of solutes in urine
- renal function
- pH of urine

### When should +ve cultures from diversions be treated?

- symptomatic infection
- culture dominant for *Proteus* or *Pseudomonas*



## Chapter 107

### • **Cutaneous Continent Urinary Diversion** •

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**What factors are important in selecting pts for continent urinary diversion?**

- ability to self catheterize
  - lack motor skills
  - lack intelligence
- **contraindications: MS, quadriplegic, very frail, mentally impaired, significant renal disease**

**How are pts prepared pre- and post-op for continent urinary diversion?**

- Pre-op
  - external stoma site selected in case of ileal conduit
  - colonoscopy if colon reservoir
  - renal and hepatic function
  - bowel prep
- Post-op
  - NG x 48h
  - TPN if NPO x >5d
  - ureteral stents out after 1 week
  - culture from each stent
  - pouchogram prior to stent removal
  - cytology after 10 years
  - colonoscopy if urine/feces mixing

**How can one classify nonorthotopic urinary diversion?**

- ureterosigmoidostomy and its variations
  - ureterosigmoidostomy
    - transplantation of ureters directly to intact fecal stream
    - used only for more last resort due to severe long-term complications
  - rectal bladder
    - ureters transplanted to rectal stump, and proximal sigmoid colon managed by terminal sigmoid colostomy
    - contraindications: dilated ureters, pelvic rads, renal insufficiency, poor anal sphincter tone, colorectal disease
  - folded rectosigmoid bladder
    - ureters anastomosed to serosal troughs, rather than into the taenia
    - 20-25cm segment of rectosigmoid folded into S shape and reconfigured
    - monitor for development of hyperchloremic acidosis: occurs in majority
  - augmented valved rectum
    - used w/ stoma appliances not available
    - similar to standard ureterosigmoidostomy, but proximal intussusception of sigmoid colon confines urine to smaller surface area
    - rectum patched w/ ileum
  - ileocecal sigmoidostomy
  - sigmoid hemi-Kock and T-pouch procedures w/ valved rectum
    - 30cm ileum selected: 10cm proximal for antireflux mechanism, 20cm for patch
    - 10-20cm distal ileum left attached to R colon, folded into V, 10cm placed in serosal lined trough
    - ureters placed into afferent limb
    - 15cm enterotomy made on anterior rectal surface, patch placed
  - sigma rectum pouch, Mainz II
    - rectosigmoid reservoir of increased capacity
    - sigmoid opened for 10-12cm, medial plate closed in 2 layers
    - ureters placed in submucosal tunnels
    - anterior wall closed in 2 layers
- continent catheterizable pouches

## Chapter 107 Questions - Catheterizable pouches.doc

- continent ileal reservoir (Kock pouch)
  - 15-20cm ileum for intussuscepted nipple valve → middle 6-8cm denuded and inverted, TA-55 used to hold
  - abandoned due to high complication rate
- double T-pouch
  - 70cm terminal ileum, divided into 10, 44, and 12-15cm segments
  - 44cm converted to W-pouch, 12cm segment tapered (forms catheterizable stoma), 10cm forms limb for ureters
- MAINZ pouch (mixed augmentation w/ ileum 'n' zecum)
  - 15cm proximal colon + 30cm TI folded to S, posterior aspects sutured to form plate
  - additional 20cm proximal ileum intussuscepted, stapled, and led through intact ileocecal valve, 3<sup>rd</sup> row of staples applied
  - initial volumes larger than in Kock or T-pouch
- R colon pouches w/ intussuscepted terminal ileum
  - UCLA pouch
    - ◆ isolate entire R colon w/ 15cm TI, colon incised along anterior taenia
    - ◆ ileum intussuscepted through ileocecal valve into cecum and stapled, absorbable mesh collar added to TI
    - ◆ pouch closed in Heinike-Miculicz fashion
  - Duke pouch
    - ◆ isolate entire R colon w/ 15cm TI, colon incised along antimesenteric border
    - ◆ patch of mucosa excised from posterior cecal plate and posterior intussusciens, sewn together to stabilize (as opposed to stapling like UCLA pouch)
  - LeBag
    - ◆ more distal ileum taken, remains intact for making nipple valve
    - ◆ nipple valve stapled to itself in 3 quadrants, no mesh collar
- Indiana pouch
  - buttressed ileocecal valve by buttressing TI → one of the most reliable reservoirs
    - ◆ interrupted Lembert sutures to doubly imbricate ileum
  - R colon opened, ureters implanted in taenia
- Miami pouch
  - similar to Indiana: more colon used, in V configuration
- Penn pouch
  - appendix serves as continence mechanism: buried in taenia
- Benckroun hydraulic ileal valve
  - poor long-term results
- gastric pouches
  - wedge of stomach w/ greatest width of 7-10cm from greater curvature
  - use L gastroepiploic preferentially as blood supply

### What are the complications of ureterosigmoidostomy?

- hyperchloremic acidosis
- hypokalemia w/ nephropathy
- pyelo
- malignancy

### What are the contraindications to ureterosigmoidostomy?

- neurogenic bladder → associated bowel or sphincter dysfunction
- dilated ureters
- renal failure
- rads
- hepatic dysfunction

### What techniques have been employed to create continence in catheterizable pouches?

- appendiceal techniques, ileocecal valve plication, or pseudoappendiceal tubes: for R colon pouches
  - appendix tunnelled into cecal taenia
- tapered or imbricated terminal ileum and ileocecal valve
  - imbrication or plication of ileocecal valve region w/ tapering of more proximal terminal ileumj
- intussuscepted nipple valve or flap valve
- hydraulic valve (ex: Benckroun nipple)
  - small bowel segment is isolated and reversed intussusception performed, apposing the mucosal surfaces of the small bowel
  - as pouch fills, pressure closes the leaves, causing continence





## **Chapter 108**

### **• Orthotopic Urinary Diversion •**

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#### **What are the long-term complication rates for ileal conduits and colon conduits?**

- Ileal conduits
  - pyelo: 16%
  - ureteroileal stenosis: 10%
  - stones: 4.5%
  - stomal stenosis: 11%
- Colon conduits
  - pyelo: 11%
  - ureterocolonic stenosis: 10%
  - stones: 4%
  - stomal stenosis: 7%

#### **What are the contraindications to continent urinary diversion?**

- Relative
  - mental or physical impairment that would preclude ability or understanding of how to perform CIC
  - limited life expectancy
- Absolute
  - permanently compromised renal function: need CrCl of 60cc/min
  - +ve frozen section of urethra at time of OR (CIS or overt carcinoma)
  - significant potential for tumour recurrence
  - if pelvic recurrence can affect functional characteristics of neobladder

#### **What form of orthotopic urinary diversion may be used for pts w/ borderline renal function?**

- gastric form of neobladder
  - excretion of Cl and H ions, beneficial in pts w/ renal failure or poor renal function
  - less mucus production

#### **Is obesity a contraindication to continent urinary diversion?**

- No: may be preferred, as obese pts have difficulty wearing urostomy appliance
  - difficulty in negotiating thick abdominal wall while performing CIC on continent reservoir

#### **What bowel segment is optimal in constructing a continent reservoir?**

- small intestine: ileum has less contractility and greater compliance
  - ileum has superior urodynamic characteristics than the colon
    - accommodates larger volumes at lower pressures than colon
    - pressure at maximum capacity lower w/ ileum
    - mucosal atrophy w/ less reabsorption of urinary constituents more reliable w/ small bowel than in large bowel reservoirs
  - colon: less compliant and may store urine at higher pressures than ileum

#### **How does one select the type of urinary diversion to be performed?**

- depends on clinical factors and pt preference
  - informed consent: risks/benefits
  - have pt talk to other pts w/ diversions
- ensure pt understands ultimate decision made intraop w/ frozen section
- colonoscopy required if large bowel to be used
  - not necessary if only small intestine used

#### **What nerves supply the urethral continence mechanism?**

- smooth muscle sphincter and BN: autonomic nerves originating in pelvic plexus

## **Chapter 108 Questions - Neobladders.doc**

- emerge from pelvic plexus and course along lateral aspect of rectum and vagina
- do not play a role in innervation of rhabdosphincter
- rhabdosphincter: branches of the pudendal nerve
- must avoid dissection along pelvic floor where branches of pudendal nerve lie

### **How does radical cystectomy affect urethral pressures?**

- abolishes normal reflex rise in urethral pressure w/ reservoir filling
- due to loss of afferent input from detrusor → not seen in RP

### **How does nerve sparing affect continence after cystectomy?**

- may be associated w/ improved urinary continence
- may be due to more careful dissection around apex w/ decreased damage to sphincteric mechanism

### **What principles of surgical technique should be followed for continence preservation during cystectomy?**

- minimal manipulation of muscle fibers of rhabdosphincter, fascial attachments, and innervation
- minimal dissection along pelvic floor levators to avoid injury to rhabdosphincter innervation
- posterior dissection should not extend distal to apex of prostate
- incise puboprostatics only enough to allow for proper apical dissection
- avoid unnecessary passage of instruments b/w dorsal complex and rhabdosphincter → may damage
- suspend dorsal venous complex anteriorly to periosteum to re-establish anterior fixation

### **What is the risk of urethral recurrence of UCC after cystectomy?**

- 10% overall
- without any urethral involvement: 6%
- superficial (mucosal and ductal) involvement: 15%
- stromal involvement: 21%

### **What are the RF for urethral recurrence after cystectomy?**

- prostatic urethral involvement (or BN involvement in women)
- **prostatic stromal invasion: strongest single predictor of recurrence after cystectomy**
- anterior vaginal wall tumour involvement (pT4 disease) → high risk of simultaneous urethral tumour (50%)
- presence of CIS → not a significant RF
- upper tract UCC → not significant

### **What is the role of prostatic biopsy prior to cystectomy?**

- may help identify men w/ prostatic tumour involvement
- identify men w/ high risk of urethral recurrence that may benefit from prophylactic urethrectomy
- low incidence of urethral recurrence if intraop frozen urethral section is -ve → may not be necessary

### **How does one manage the pt w/ -ve frozen sections and prostatic stromal tumour involvement on final path?**

- cutaneous urinary diversion (conduit/reservoir): delayed urethrectomy
- orthotopic diversion: monitor closely w/ urethral washings for cytology

### **What is the risk for pelvic recurrence of UCC after cystectomy?**

- 7% overall
- organ confined LN -ve disease (T2N0): 5% local recurrence
- non-organ confined LN -ve disease (T3N0): 10% local recurrence
- LN +ve disease (TxN1): 11% local recurrence

### **What becomes of neobladder function after pelvic recurrence?**

- usually normal neobladder function until death

### **What is the role of neobladder after salvage cystectomy?**

- is an option for well-selected pts after rads and cystectomy
- UI rates after cystectomy are significant: may need AUS in 25%

### **What are the arguments for and against antireflux mechanisms in orthotopic diversion?**

- Against
- neobladder should accommodate large volumes at low storage pressures
- urine should be sterile

## Chapter 108 Questions - Neobladders.doc

- complete emptying performed w/ Valsalva
  - Valsalva should increase pressure equally in ureter and bladder, preventing reflux
- antirefluxing system creation is more challenging
- antirefluxing mechanism may be associated w/ higher complications
  - obstruction
- harmful effects of VUR only seen in animal models
- good results seen w/ Studer limb
  - need 60cm ileum for Studer limb
- For
  - preventing reflux is important in protecting upper tracts
  - significant indirect evidence to support need for antireflux device
  - antireflux mechanisms are effective and have few complications
  - bacteriuria common in pts w/ orthotopic bladders w/ potential for high intrareservoir voiding pressures (80-150cm H<sub>2</sub>O)

### How long does it take for upper tract deterioration after diversion?

- may take 10-20yrs
  - may occur even in face of normal radiographic studies

### What complications are seen w/ the intussuscepted afferent nipple valve?

- calculi: on exposed staples: 5%
- afferent nipple stenosis: 4%
- extussusception (prolapse of afferent limb): 1%

### What is the role for an antireflex mechanism in continent cutaneous reservoirs?

- required: chronically infected

### What are the advantages of the serous lined tunnel antireflux mechanism?

- less bowel needed: only 40cm ileum
  - fewer metabolic complications
- metallic staples not needed
- ureters can be anastomosed w/ low incidence of strictures
- not challenging or time-consuming

### What techniques of orthotopic bladder substitutes are available?

- Camey II
  - 65cm ileum isolated and bowel integrity restored
  - ileum detubularized and folded in U shape (or Z shape)
  - fingertip opening made in middle for anastomosis to urethral stump
- Vesical ileal pouch (VIP pouch)
  - like Camey II, but more spherical
  - 60cm ileum, closed in jelly-roll (croissant) fashion
- S-Bladder
  - 75cm ileum isolated and arranged in S shape
  - ileum detubularized except for distal 5cm and proximal 15cm
  - proximal 15cm converted to afferent antireflux Kock nipple
  - ureters spatulated and anastomosed to antireflux nipple
  - distal ileum tapered down to urethra and anastomosed
- Ileal neobladder (Hautmann)
  - 70cm terminal ileum placed in W shape and entire segment opened
  - small fingertip opening made and anastomosed to urethra
  - ureters implanted from outside through small incision in ileum at convenient point (LeDuc style)
- Studer ileal bladder substitute
  - ileal bladder w/ long afferent isoperistaltic tubular ileal segment
  - 54-60cm terminal ileum isolated 25cm proximal to ileocecal valve
  - distal 40cm placed in U shape and opened
  - ureters spatulated and anastomosed in end-to-side fashion to proximal afferent tubular portion of ileum
  - distal ileum sewn together in U shape, then folded back on itself to make sphere
  - hole cut out of dependent portion and anastomosed to urethra
- Orthotopic Kock ileal reservoir

## Chapter 108 Questions - Neobladders.doc

- intussuscepted nipple valves for both afferent (antireflux) and efferent (continence) limbs
- 61cm terminal ileum isolated, 2 x 22cm segments placed in U shape and opened and sewn together
- 5-7cm antireflux nipple valve created
- Serous-lined extramural tunnel
  - 40cm ileum isolated and arranged in W shape and edges of medial flap joined
  - 2 lateral flaps joined by seromuscular continuous 3-0 silk
  - each ureter laid in 2 lateral troughs, and mucosa-to-mucosa anastomosis performed
  - mucosal edges of 2 lateral flaps joined over top of ureters
  - suture line inferiorly opened to make a hole for urethra
- T-pouch ileal neobladder
  - same configuration as Kock pouch, w/ different antireflux technique
  - maintain vascular arcades by opening windows of Deaver → allows segment of ileum within serous lined trough to create fla valve
  - 44cm distal ileum placed in inverted V shape (2 x 22cm) w/ another segment of proximal 8-10cm preserved (or longer if short ureters)
  - proximal end of isolated segment closed
  - anchor distal 3-4cm afferent ileal segment into serous lined trough
  - open mesenteric windows of Deaver b/w vascular arcades → allows permanent fixation of isolated segment in trough
  - taper distal segment of proximal ileum in trough to 30F
  - incise ileal mucosa over tapered segment to complete posterior wall
  - reservoir folded over and closed in opposite direction
  - leave dependent portion open to anast to urethra
- Orthotopic MAINZ pouch
  - MAINZ (**m**ixed **a**ugmentation ileum '**n**' **z**ecum)
  - 10-15cm cecum + 20-30cm terminal ileum opened and sewn in S shape
  - tunneled ureterocolonic anastomosis
  - buttonhole in most dependent portion of cecum for urethra
- Ileocolonic (Le Bag) pouch
  - 20cm ascending colon + 20cm terminal ileum and sewn in V shape
  - reservoir rotated 180° into pelvis w/ most proximal portion of ileum sewn to urethra
- R colon pouch
  - entire R colon and cecum isolated and opened along anterior taenia, leaving proximal 2-3" of colon intact
  - appendectomy performed, ureters implanted, colon folded over
- Sigmoid pouch
  - 35cm descending colon isolated and sewn in U fashion
  - ureters implanted in antireflux tunnels
  - small buttonhole in most dependent portion of reservoir

### How are these pouches managed postoperatively?

- 24F pouch catheter irrigation
- bilateral ureteric stents x 1-2wks
- pelvic drain: 1" Penrose
- Hemovac drain x 24h postop
- need urethral surveillance
  - palpate urethroenteric anastomosis via pelvic exam or DRE
- **voided cytology on each visit postop**

### What are the advantages of the T-pouch?

- no exposed staples
- complete preservation of blood supply to entire afferent ileal segment
  - prevents nipple stenosis
- serous lined tunnel protects implanted ileum from exposed urine, allowing healing w/o scar
- can be created w/ short ureters
- can be created w/ large-caliber or dilated ureters

### What are the results from orthotopic neobladder series?

- no significant difference in perioperative mortality and complication rate vs. different forms of diversion
  - 3% mortality rate overall
- early complications: 5-15%



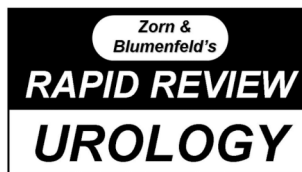
### **Chapter 108 Questions - Neobladders.doc**

- late complications: 10-25%
- continence: 80-90%

#### **What is the QOL like after orthotopic neobladder vs. conduits?**

- ileal conduit pts have poorest self-image
- pts converting from conduit → neobladder most satisfied
- health related QOL maintained most in neobladder pts
- long-term: no difference in QOL among diversions  
→ all studies have methodologic problems





## Chapter 109

### • Surgery of the Seminal Vesicles •

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#### What is the physiologic role of the SVs?

- important in motility and metabolism of ejaculated sperm
- secretions from SV contribute 50-80% of ejaculate volume

#### What is the female homologue of the SV?

- none → male only

#### Describe the anatomy of the SV.

- 5-10cm long, 3-5cm diameter
- one central canal w/ minimal tortuosity, few side branches: most common
- blood supply from vesiculodeferential artery (branch of umbilical)
- venous drainage to vesiculodeferential veins and inferior venous plexus
- innervated by pelvic nerve and hypogastric nerve

#### What are the sx of SV neoplasms?

- usually asymptomatic
- retention, dysuria, hematuria, hematospermia
- SVs not palpable in normal male

#### What are the findings on TRUS consistent w/ SV obstruction?

- AP diameter > 15mm
- length > 35mm
- large anechoic areas containing sperm on aspiration

#### What anomalies are associated w/ SV agenesis?

- unilateral: 0.6-1% incidence
  - associated w/ unilateral absence of the vas, ipsilateral renal anomalies
  - if insult before 7weeks (separation of ureteric bud from mesonephric duct), will be associated w/ renal anomalies
- bilateral
  - associated w/ CBAVD + CFTR gene mutations
  - 70-80% of men w/ CBAVD have CF mutation, and 80-95% of men w/ CF have CBAVD or SV agenesis

#### What is the etiology of vesiculitis?

- colonic flora: due to bacterial prostatitis

#### What is the etiology of SV abscess?

- usually unknown
- RF: DM, catheters, endoscopic manipulation

#### What is the treatment of SV abscess?

- open drainage

#### What are the sx and tx of SV stones?

- present w/ pain, infection, hematospermia, infertility
- tx w/ open vesiculectomy + antibiotics

#### What is the DDx of a SV mass?

- Benign
  - cysts: due to ED obstruction
    - tx w/ transperineal drainage if symptomatic or open excision

## Chapter 109 Questions - SV.doc

- abdo US in all pts w/ SV cysts to r/o ADPKD
- papillary adenoma/cystadenoma
- mimic SV cysts, occur in middle-aged men unilaterally → remove
- fibroma
- leiomyoma
- amyloid: SV deposits in 4-17%
- Malignant
- adenocarcinoma
- sarcoma

### What d/o are related to SV cysts?

- renal agenesis, infertility, hematospermia, GU infection, ADPKD

### What are the characteristics of a primary SV adenocarcinoma?

- > 50 yrs
- extend locally into prostate/bladder/rectum
- prostatic +/- ureteral obstruction
- mucin-producing papillary or anaplastic carcinoma on TRUS/bx
- normal serum markers for prostate ca (PSA, PAP)
- **elevated CEA**

### What is the treatment of a solid lesion in the SV?

- benign: tx depends on sx
- asymptomatic: repeat TRUS
- enlarges, sx: simple SVectomy
- malignant: mass large, questionable margins, malignant columnar or poorly differentiated carcinoma cells
- cystoprostatectomy w/ PLND
- no role for adjuvant therapy

### What are the indications for operating on the SVs alone?

- transperineal/transvesical aspiration of SV cyst/abscess
- transurethral unroofing of SV cyst/abscess
- lap dissection
- open resection of one or both SV

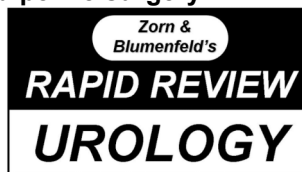
### Describe the various approaches to operating on the SVs.

- Open
- Transperineal: for pts w/ chronic seminal vesiculitis → limits ability to reach more than a few cm above BN
- similar to RPP
- dissect rectal wall free and release high on base of prostate
- incise Denonvilliers' transversely above level of the base of the SVs on the prostate
- dissect Denonvilliers' laterally away from SV and ampulla
- 2 ampullae dissected directly above prostate
- wide resection including vas for carcinoma
- pass R angle clamp around SV and use 2-0 to ligate stump
- Allis clamp placed on cut edge to pull, Metz to free SV from surrounding tissue
- Penrose drain left
- Transvesical
- midline extraperitoneal SP incision made up to umbilicus, separate rectus muscles
- open bladder longitudinally for 7-10cm, ending 2-3cm away from BN
- place feeding tubes into ureters
- incise through trigone vertically for 5cm
- ampullae of vas seen under BN
- identify SVs lateral to ampullae, encircled and dissected free
- clip proximal end, tie distal end and remove from field
- close bladder w/ 2-0 running and 4-0 running (2 layers) ant and post
- place suction drain
- Paravesical: used in children for large unilateral cysts lateral to and above the bladder, or if NUU required
- midline or Pfannenstiel incision
- bladder finger dissected away from lateral sidewall

## Chapter 109 Questions - SV.doc

- vas identified, placed on tension, and dissected down to base of bladder
- dissect b/w bladder and cyst
- identify ureter as it crosses vas
- sacrifice superior vesical artery and inferior vesical artery if needed
- stay directly on mass as approach, to prevent NVB injury lateral to SV
- clip and tie SV and transect
- Retrovesical: use in pts requiring bilateral SV excision for mass or cysts
  - midline SP incision
  - dissect peritoneum from dome of bladder
  - bladder dissected antegradely from rectum until SV and ampullae seen
  - SVs dissected down to base of prostate and ligated and divided
  - ampullae not taken
- Transcoccygeal: used in pts not able to maintain perineal or supine position, or w/ multiple SP or perineal surgeries
  - pt prone in jackknife position
  - incision made in L shape from midway on sacrum (10cm from tip of coccyx) and angled at tip of coccyx down gluteal cleft within 3cm of anus
  - coccyx dissected free from underlying rectum
  - gluteus maximus layers moved aside
  - lateral wall of rectum on side of lesion dissected medially from levators until prostate seen
  - dissect tissue directly superior to base on midline should show ampullae and SVs
- Endoscopic/Laparoscopic
  - TUR
    - if cyst adjacent to prostate, can unroof w/ deep TUR
    - distal to BN at 5 or 7 o'clock position
  - Laparoscopic
- Sclerotherapy: tetracycline





## Chapter 110

### • Surgery of the Penis and Urethra •

---

#### **What is the definition of a graft?**

- implies that tissue has been excised and transferred to a graft host bed
- new blood supply will be established by a process called *take*

#### **What are the phase of graft take?**

- imbibition: 1<sup>st</sup> 48 hrs, graft survives by drinking nutrients from adjacent graft host bed
- inosculation: 2<sup>nd</sup> 48 hrs, true microcirculation re-established in graft

#### **How does the thickness of a graft affect graft take?**

- STSG
  - interface b/w epidermis and dermis (or epithelium and lamina) contains superficial plexus
    - contains lymphatics, numerous vessels
  - graft carries epidermis, exposes superficial dermal plexus → favourable vascular characteristics
  - few lymphatics: more brittle, less durable, tends to contract
  - can be meshed to allow subgraft collections to escape
- FTSG
  - carries epidermis and full dermis/lamina + deep plexus
  - deep plexus has larger vessels → more sparsely distributed → less favourable vascular characteristics
  - does not contract, more durable when mature
  - rarely meshed: only for preputial or penile skin, or burn coverage

#### **What donor graft sites are available for GU procedures and how does this affect take?**

- bladder epithelial graft
  - superficial and deep plexus connected by many more perforators than dermal graft
    - favourable vascular characteristics
- buccal mucosal graft
  - panlaminal plexus
    - optimal vascular characteristics
    - can be thinned
- dermal graft
  - takes readily and has normal skin properties
- tunica vaginalis graft
  - essentially peritoneum
  - useful for small defects of tunica albuginea of the corpora cavernosa
  - tend to form aneurysmal dilation when used for larger defects
- vascular graft
  - not true grafts
  - survives by endothelial direct perfusion and re-establishment of vein wall blood flow by perfusion of vasa vasorum
  - used widely for replacement of defects in tunica albuginea of corpora cavernosa

#### **What is the definition of a flap?**

- implies that tissue is excised and transferred with the blood supply either preserved or surgically re-established at the recipient site

#### **What are the different types of flaps?**

- random flap: flap w/o defined cuticular vascular territory
- axial flap: defined vessel in base of flap
  - direct cuticular axial flap: flap based on vessel superficial to the superficial layer of the deep body wall fascia (ex: groin)
  - musculocutaneous flap: based on vascularity to muscle

## Chapter 110 Questions - Urethras.doc and penile surgery

- fasciocutaneous flap: deep blood supply carried on fascia and overlying skin based on perforators
- peninsular flap: vascular and cutaneous continuity of the flap base are left intact
- island flap: vascular continuity maintained, but cuticular continuity divided
- microvascular free transfer flap: vascular continuity reestablished at recipient site

### What are the five "sphincters" present in the urethra?

- bladder neck
- prostatic muscular stroma
- intrinsic sphincter of prostatic urethra
- external sphincter (rhabdosphincter)
- muscles of recruitment in membranous urethra

### Describe the vascular supply to the penis.

- Arterial
  - Skin: superficial external pudendal → superficial penile a.
    - arise from first portion of femoral artery, divide into 2 main branches (dorsolateral and ventrolateral)
    - lies in the superficial fascia of the penis overlying Buck's
    - extend into prepuce: spread circumferentially and turn back to terminate near corona
  - Deep structures: internal pudendal → common penile artery → 3 branches:
    - bulbourethral artery: supplies spongiosum, urethral bulb, and glans
    - dorsal artery: supplies glans mostly (few branches into cavernosae)
    - cavernosal artery → gives off multiple helicine arteries
  - internal pudendal → common penile + perineal artery (supplies scrotal skin via posterior scrotal artery)
- Venous – 3 systems:
  - superficial: superficial dorsal vein → L saphenous vein
  - intermediate: subtunical venular plexus (at periphery, collect blood from sinusoids) → emissary veins → circumflex veins → deep dorsal veins (w/i Buck's) + periurethral veins → Santorini's plexus → vesical plexus and internal iliac veins
  - deep: crural, cavernosal, and bulbar veins → internal pudendal veins → internal iliac vein (through Alcock's canal)
- Lymphatics
  - glans → large trunks in frenulum → traverse beneath Bucks → terminate in deep inguinal LN of femoral triangle

### What glands empty into the male urethra?

- prostate gland
- glands of Littre open into urethra along dorsal surface
  - more numerous distally and less proximally
  - form small diverticulae: lacunae of Morgagni
- Cowper's glands (bulbourethral glands)
  - open into urethra in bulb and travel into glands located in urogenital diaphragm

### Describe the nerve supply to the penis.

- Peripheral
  - Autonomic
    - Sympathetics
      - ◆ sympathetics originate from T10/11-L2
        - ◆ pass through white rami → sympathetic chain ganglia
      - ◆ T10-T12 fibers pass through lumbar splanchnic nerves to aorticorenal ganglion and inferior mesenteric ganglion
      - ◆ L1-2 fibers pass through 3<sup>rd</sup> and 4<sup>th</sup> lumbar splanchnic nerves to superior hypogastric plexus
        - ◆ pass to superior hypogastric plexus, hypogastric nerves, then inferior hypogastric (pelvic) plexus, join w/ parasympathetics
        - ◆ go to vesical plexus, then cavernous nerves
      - ◆ responsible for detumescence
    - Parasympathetics
      - ◆ preganglionic fibers arise from neurons in intermediolateral cell columns of S2-4, pass through pelvic splanchnic nerves (nervi erigentes) to pelvic plexus (inferior hypogastric plexus) → vesical plexus → cavernous nerves
        - ◆ joined by sympathetic nerves to form ?superior hypogastric plexus
      - ◆ stimulation of parasympathetics causes erection
  - Somatic



## Chapter 110 Questions - Urethras.doc and penile surgery

- thin myelinated A<sub>δ</sub> and unmyelinated C fibers originating in skin, converge to form dorsal nerve of penis
- becomes pudendal nerve, passes under sacrospinous ligament and over sacrotuberous ligament, runs through Alcock's canal, and enters cord at S2-4
  - ◆ terminates in central gray region of lumbosacral segment
- responsible for sensation and contraction of bulbocavernosus and ischiocavernosus
- main cutaneous supply comes through the dorsal and posterior branches of the pudendal nerve
  - ◆ anterior scrotum and proximal penis supplied by ilioinguinal nerve
- Supraspinal
  - medial preoptic area and paraventricular nucleus of hypothalamus and hippocampus integrate sexual function and erection
  - cerebral impulses travel through sympathetics (?inhibitory interneurons to inhibit NE release), parasympathetic (to release NO and ACh), and somatic (to release ACh) to produce erection

### What is the typical presentation for a urethral hemangioma?

- hematuria or bloody urethral d/c
- occasionally obstructive sx
- lesions single or multiple, commonly at meatus

### What is the treatment for a urethral hemangioma?

- depends on size and location
  - asymptomatic: observe → may regress
  - smaller lesion: laser (KTP or Nd:YAG)
  - larger lesion: open excision and urethral reconstruction

### What is the typical urethral involvement by Reiter's?

- urethritis usually mild, self-limiting
- glandular lesion in 10-20% → **circinate balanitis**
  - shallow painless ulcer w/ gray borders
  - small red macules 1-2mm diameter
- no tx if mild and self-limiting
- if severe inflammation and necrosis of mucosa + stricture → tx w/ perineal urethrostomy and complete distal urethral excision

### What is BXO?

- genital lichen sclerosus et atrophicus
- characterized by hyperkeratosis, homogenization of collagen in papillary dermis + stromal edema and lymphocytic infiltrate
- appears as a whitish plaque that may involve the prepuce, glans, meatus, and fossa
  - usually spares proximal anterior urethra
- can involve skin of penile shaft
- may present as buried penis

### What microorganism has been associated w/ BXO?

- *Borrelia burgdorferi* (spirochete)

### What is the treatment for BXO?

- foreskin only: circ
- glans and meatus: topical steroids (0.1% triamcinolone) and antibiotics (erythromycin), CIC
- young pt, severe meatal stenosis: penile island flap
  - RUG prior to treatment: may have more proximal disease
  - ? buccal graft to prevent recurrence
- overweight, complex: reconstruction vs. PU
- observe for SCC

### What are the causes of urethrocutaneous fistulae?

- complication of urethral surgery
  - early
    - poor local healing: hematoma, infection, tension
  - late
- periurethral infection

## Chapter 110 Questions - Urethras.docand penile surgery

- tx of urethral growth

### What is the management of urethrocutaneous fistulae +/- periurethral abscess?

- fistulae as complication post-urethral surgery
  - cystoscopy
  - urinary diversion w/ Foley in some cases
  - repair of fistula: delayed for minimum 6mo
    - small: button of skin removed from around fistula and urethra closed primarily w/ 6-0 or 7-0 PDS
    - large: trapdoor of penile skin left attached to one end of fistula, sewn into place
- fistulae associated w/ inflammatory strictures
  - occur as periurethral tracts and develop due to high-pressure voiding of infected urine
  - Immediate
    - stabilize pt: BP/HR, correct BS/acid-base abnormalities
    - place on antibiotics: broad spectrum, switch once cultures back
    - I&D of abscess
      - ◆ modified dorsal lithotomy position
      - ◆ EUA to assess extent of disease and to ensure GI tract (rectum) not involved
      - ◆ urinary diversion w/ SP tube (do NOT instrument urethra → full-blown sepsis possible)
      - ◆ drainage of abscess (longitudinal incision in penis to avoid lymphatic injuries)
      - ◆ debride all non-viable tissue
      - ◆ biopsy tissue to r/o cancer
      - ◆ identify urethral defect: 1<sup>st</sup> stage urethroplasty done if possible (perineal urethrostomy)
    - dressing changes, overall health & nutrition
  - Delayed (wait 4-6mo)
    - treat underlying conditions (DM, etc.)
    - dressings and packing until clean, granulating, and healed
    - RUG + VCUG + cysto
    - Management of stricture:
      - ◆ VIU likely insufficient due to pan-urethral disease (spongiofibrosis)
      - ◆ Urethroplasty
        - ◆ One-stage procedure
        - ◆ Two-stage repair with initial perineal urethrostomy
      - ◆ Skin/wound coverage

### What is the etiology of a urethral diverticulum?

- distension of a segment of urethra
- attachment of a structure to urethra by narrow neck (Mullerian remnant)
- congenital diverticulum of prostatic urethra
  - large utricle
- female: dilation of periurethral glands, following birth trauma

### What is the presentation and management of the urethral diverticulum?

- Sx
  - **3 D's: dribbling, dysuria, dyspareunia**
  - urethral dribbling after voiding
  - pain if infected
  - palpation of mass
  - expression of urine or infected material
- Management
  - dx: US or MRI
  - excise diverticulum and closing its neck through vertical or U-shaped vaginal incision
  - classically lateral to urethra

### What factors may cause relative shortening, dorsal chordee, or penile torsion after a W-flap reconstruction in a patient w/ exstrophy?

- scar tissue attaching the penis to the anterior pelvis or fascia
- shortness of a dorsally placed native urethra or scarring of a previously placed neourethra
- inelasticity of abnormal attachments of the deeper dartos and Buck's
- inelastic or dysgenetic dorsal tunica albuginea

## **Chapter 110 Questions - Urethras.doc and penile surgery**

### **Why must 2 needles be used to create an artificial erection in patients w/ exstrophy or epispadias?**

- corpora in exstrophy or epispadias do not communicate

### **What are the treatment options to correct chordee in pts w/ exstrophy or epispadias?**

- excision of ellipses of tunica from the ventral corpora
- inward corporal rotation
- lengthen dorsal corpora w/ dermal graft
  - avoid synthetic grafts

### **What are the options for urethral reconstruction in exstrophy?**

- flap of ventral penile skin can be tubed
- tubed graft can be brought to the ventral penis by bringing it b/w the corporal bodies
  - graft options: penile/preputial skin, bladder epithelium, buccal mucosa

### **Why is there no umbilicus in pts w/ exstrophy?**

- cord enters from the upper edge of the exstrophic bladder patch

### **Describe the management of amputation of the penis.**

- If distal penis available
  - amputated penis cleaned, wrapped in sponge in NS, placed in sterile Ziploc, kept in ice slush
    - reimplant up to 18 hrs
  - urethra, corpora cavernosa, and dorsal NVB exposed and debrided
  - 2 layer spatulated urethral anastomosis
  - repair tunica albuginea w/ interrupted sutures
  - microvascular repair of dorsal vein, deep dorsal artery, dorsal nerves
  - coverage w/ native skin
  - divert w/ SP tube
  - stent urethra
- If distal penis unavailable
  - close corporal bodies w/ 4-0 or 5-0 PDS
  - spatulate urethral meatus to tunica
  - cover penile shaft w/ STSG if skin coverage needed

### **Why do degloving injuries to the penis usually not bleed?**

- tear is deep to elastic dartos fascia
- not many large vessels in this space

### **How does one manage degloving injuries of the penis?**

- dress wounds in SS bandage
- immediate reconstruction w/ STSG to penile shaft
- suture testes together in midline, cover w/ meshed STSG
  - tunica vaginalis opened, graft placed directly on testicles
  - STSG more successful as weight of testes gradually makes skin more redundant
- do not replant avulsed testes, due to stretch injury to spermatic vessels

### **How does one manage genital burns?**

- careful debridement
- corporal tissue cannot be replaced w/ transferred tissue
- urethral reconstruction may be needed
  - PU often needed during transfer of vascular tissues to the area of perineum and penis

### **What groups of patients suffer radiation trauma to the penis?**

- pts w/ radiation tx for lesion on penis
- pts w/ radiation to pelvis w/ chronic lymphedema

### **How does radiation trauma from pelvis rads affect the penis?**

- lymphedema
- cellulitis
- weeping of fluid
- lymphangectasia

## Chapter 110 Questions - Urethras.docand penile surgery

### What principles of repair should be followed in the reconstruction of pts w/ lymphedema of the genitals?

- excise lymphedematous tissue by removing dartos fascia and skin, dissecting superficial to Buck's  
→ Colles' fascia/dartos and scrotal skin removed
- fix testes in midline
- cover penile shaft w/ STSG → FTSG will reaccumulate lymphedema
- cover testes w/ meshed STSG if cannot close scrotum
- avoid local skin flaps: poor cosmetic results and often reaccumulate lymphedema

### What is the definition of urethral stricture disease?

- scarring process involving the spongy erectile tissue of the corpus spongiosum (spongiofibrosis)  
→ posterior urethral "strictures" are not included in common definition of urethral stricture, as due to RP or trauma

### What is the etiology of urethral stricture?

- any process that injures the urethral epithelium or sponge
  - trauma
    - iatrogenic: instrumentation
    - straddle injury (anterior) or pelvic # (posterior)
    - self-induced
  - inflammation/infection
    - gonorrhoea, chlamydia
    - BXO
      - ◆ high pressure voiding, causing intravasation of urine into glands of Littre + inflammation, abscesses, + fibrosis
  - congenital: at location where fusion of posterior and anterior urethra → short-length, not inflammatory, no hx trauma
  - neoplastic: urethral ca
  - idiopathic

### How do pts w/ strictures present?

- obstructive voiding sx
- UTI: prostatitis, epididymitis
- retention

### How can one evaluate the extent of urethral strictures?

- must determine location, length, depth, and density of stricture
- radiography: RUG/VCUG
  - extravasation may occur if inflammation
  - need oblique shots
- urethroscopy/bougienage
  - not necessary or beneficial to dilate the stricture at the time of initial cysto
  - evaluate urethra completely proximally and distally to stricture during OR
  - **never perform blind filiforms and dilation**
- US
  - may more accurately determine stricture length

### What are the options for treatment of urethral stricture disease?

- Conservative
  - Catheter: CIC vs. indwelling or SP
  - VIU: cold vs. laser
  - Dilation: self or not
  - Stent
- Open reconstruction (urethroplasty)
  - excision and reanastomosis
  - excision and tissue transfer
    - flaps (generally onlay flaps)
      - ◆ penile (ventral): for proximal penile or some bulbar strictures
      - ◆ preputial (dorsal, transverse island): for distal strictures
      - ◆ scrotal island → hairless: for proximal penile or bulbar strictures
      - ◆ perineal

## **Chapter 110 Questions - Urethras.doc and penile surgery**

- grafts: bladder, buccal, skin (STSG/FTSG)
  - ◆ 1 stage vs. 2 stage
  - ◆ anterior vs. posterior
- urinary diversion
  - perineal urethrostomy alone
  - BN closure and complete diversion

### **Why use PDS vs. Vicryl in urethral reconstruction?**

- PDS: hydrolysed
- Vicryl: phagocytosed w/ inflammation

### **What are the characteristics of a neoplastic cause of urethral stricture?**

- hx of chronic or recurrent stricture
- failure post-op
- vascular stricture
- periurethral mass

### **What is the goal of stricture dilation?**

- to stretch the scar w/o producing more scarring
  - if bleeds, it has been torn, and will further injure the area

### **Where does one cut the stricture during a VIU?**

- single incision at 12 o'clock
  - careful: thinnest part of the sponge is from 10 to 2 o'clock
  - urethral arteries at 3 and 9 o'clock

### **What are the complications of VIU?**

- Early
  - bleeding
  - infection: periurethral abscess
  - extravasation of irrigant
  - false passage
- Late
  - ED due to local cavernosal veno-occlusive dysfunction
  - recurrence of stricture
  - incontinence: if damage external sphincter
  - urethral diverticulum

### **What is the cure rate for VIU?**

- 20-35%: reported as successful if offers temporary relief

### **What factors will help w/ success rate of VIU?**

- short stricture length: stricture of bulbous urethra < 1.5 cm
- superficial stricture: not associated w/ dense, deep spongiofibrosis
- post-VIU stenting: leave catheter x 3-5d or CIC after VIU x 3-6months

### **How does the length of catheterization affect success for VIU?**

- no effect: 3-7 days equivalent to 6 weeks, neither enough to counter effects of wound contraction

### **What are the complications of permanently implantable stents?**

- pain: w/ sitting, erection, intercourse → if placed beyond the area of the scrotal urethra
- stent migration
- post-void dribbling, incontinence

### **What are the contraindications to the Urolume stent?**

- Absolute
  - prior substitution urethral reconstruction
    - severe virulent hypertrophy of skin w/ recurrence of stricture
  - deep spongiofibrosis: urethral distraction and straddle injuries
    - posterior urethral distraction injury specifically contraindicated in product insert

## Chapter 110 Questions - Urethras.docand penile surgery

- location of stricture:
  - meatal stricture
  - penile urethral stricture
  - distal anterior urethral stricture
  - bulbar urethral stricture that cannot be opened to 26F by VIU or dilation
  - stricture of external sphincter
- active UTI
- urethral condition requiring transurethral manipulation w/i 8 weeks of UroLume placement
- infected suppurating strictures
- fistula at proposed prosthesis site
- urethral cancer
- perineal urethrostomy
- Relative
  - pt < 50 yrs
  - no medical contraindication to open reconstruction

### What lasers have been used to treat urethral strictures?

- CO<sub>2</sub>, Argon, KTP, Nd:YAG, Ho:YAG, excimer
  - no difference in results vs. cold knife

### What is the most dependable technique of anterior urethral reconstruction?

- complete excision of area of fibrosis w/ primary reanast of normal ends of urethra

### What technical points should be followed during excision and reanastomosis for urethral stricture?

- area of fibrosis totally excised
- urethral anast widely spatulated
- anast tension-free
  - **requires vigorous mobilization of the corpus spongiosum**

### What is the maximal length of stricture that can be treated w/ excision and reanastomosis?

- 1-2 cm easily excised, max 3-4 cm
- further proximal the stricture is, longer it can be and still be reconstructed w/ anast

### What grafts have been used for urethral reconstruction?

- FTSG, STSG
- bladder epithelial graft
- buccal mucosal graft

### What are the various locations for performing a graft onlay?

- ventral onlay with spongioplasty (sponge closed over graft)
  - spongioplasty requires spongiosum next to area of the stricture to be N and non-fibrotic
- lateral onlay w/ quilting to ischial cavernosal muscle
  - allows exposure of urethra while cutting through spongiosum → thinner, limits bleeding and maximizing exposure
- dorsal onlay w/ spread fixation to the graft
  - to try to improve graft bed immobilization and approximation

### Describe the Monseur technique of urethral reconstruction, and its Barbagli modification.

- urethrostomy created through the stricture on the dorsal wall
- edges of the stricture sutured open to the underlying triangular ligament or corpora cavernosa or both → **no graft**
- Barbagli mod: in area of urethrostomy, **graft applied** to triangular ligament, and stricture edges sutured to edges of graft

### Describe the technique of a 2-stage mesh graft urethroplasty.

- 1<sup>st</sup> stage
  - strictured urethra is excised completely
  - dartos fascia mobilized and brought in to cover tunica albuginea and scar in defect w/ vascularized tissue
    - if graft placed immediately on tunica albuginea, cannot mobilize in 2<sup>nd</sup> stage to create tube
  - STSG harvested from buttocks or inner surface of the thigh and meshed
    - placed in site of excised urethra as open-faced graft, w/o expanding mesh
  - graft covered w/ gauze and bolster of batting w/ tie-over sutures, Foley left in proximal urethra
- 2<sup>nd</sup> stage: 1yr later (some ppl wait only 3-4mo)

## Chapter 110 Questions - Urethras.docand penile surgery

- proximal and distal portions of the urethra evaluated w/ bougies and cysto
- catheter passed into bladder
- 3cm wide strip marked to form new urethra, outlining flaps at each end to tailor junction of tube to existing urethra
- dissection carried out laterally to mobilize remaining skin
- approximate neo-urethral edges w/ interrupted sutures, w/ knots in lumen
- 2<sup>nd</sup> layer w/ running sub-epithelial monofilament to roll edges in
- skin closed
- suction drain
- SP tube

### What are the important considerations for the use of flaps in urethral reconstruction?

- nature of the flap tissue
- vasculature of the flap
- mechanics of flap transfer

### What are the options for flaps in urethral reconstruction?

- dorsal skin island mobilized on dorsal dartos fascia
  - if redundancy is dorsal
- ventral longitudinal skin island
  - if redundancy is ventral
  - may be extended into meatus for distal strictures
- circular skin island
- combination of stricture excision w/ skin island onlay or graft onlay (augmented anastomosis)
- urethral excision w/ graft or skin island onlay
  - **cannot use skin island w/ BXO → buccal graft only**
- epilated midline genital skin island
  - must be laterally based
  - perform w/ narrow-gauge needle and monopolar cautery or epilation machine
  - urethral reconstruction 10-12 weeks later

### Describe the technique of a urethral longitudinal skin island (Orandi) flap.

- primary incision full thickness through dartos fascia and superficial Buck's fascia lateral to corpus spongiosum
- dissection to elevate the dartos fascial flap past spongiosum in midline
- lateral urethrotomy entire length of the stricture
- undermine skin lateral to skin paddle, creating longitudinal skin island
- medial edge of flap fixed to urethrotomy
- flap inverted into defect
- watertight subepithelial suture line completed w/ running absorbable monofilament
- close skin w/ subcutaneous and cutaneous sutures

### Describe the technique of a longitudinal skin island flap used to treat distal stricture disease extending into the meatus.

- spongiosum exposed
- urethrostomy performed into meatus
- skin island elevated aggressively on dartos flap to reach into meatus
- skin island affixed to one side of urethrotomy
- flap inverted w/ contralateral suture line tacked
- close ventral penis

### What techniques are available for reconstruction of the fossa navicularis?

- dilation or meatotomies
  - seldom successful
- spatulation of random penile skin flaps into the meatotomy defect: often poor cosmesis
  - Blandy: small longitudinal penile skin flap brought into defect
  - Brannen: midline random flap brought into defect
  - Cohney: transverse random flap brought into defect
  - DeSy: ventral longitudinal skin island advanced into defect, w/ de-epithelialization of portion of flap
  - Devine: stenotic fossa excised, FTSG tubularized to replace fossa
- skin island flaps elevated on dartos (Jordan)
  - ventral corpus spongiosum exposed and urethra opened ventrally through area of stenosis

## Chapter 110 Questions - Urethras.docand penile surgery

- transverse ventral skin island elevated on ventral dartos fascia
- skin island transposed and inverted into meatotomy defect
- skin closed over flap

### How should one deal with the stricture due to BXO?

- staged buccal graft techniques
  - very high recurrence rate
  - use of skin as flap or graft does not prevent recurrence in reconstruction

### How does one evaluate urethral distraction injuries?

- Initial assessment
  - Trauma assessment: ABC's, ensure hemodynamically stable
  - History of injury: mechanism of injury, pain, ability to void since, blood per meatus or hematuria
  - GU history: voiding symptoms, strictures, BPH, TUR surgery
  - Physical: VS, temp, palpable bladder, CVAT, abdomen, perineal and scrotal bruising, blood at meatus, DRE for high-riding prostate
  - Lab: U/A, urine C&S, CBC
- Define precise anatomy of distraction defect: location & length
  - **do not insert Foley**
  - contrast studies: cystogram, RUG
  - endoscopy through SP tract
  - if radiologically complete injury, then options are to:
    - Insert SP tube, let injury settle, reassess and treat accordingly
    - Gently attempt to pass catheter into bladder
    - Attempt to insert catheter endoscopically
- 4-6 months later
  - RUG and VCUG to assess stricture
  - If short bulbar urethral stricture → tx w/ VIU
    - Urethroscope with urethrotome
    - Identify stricture, if tight use wire or ureteral catheter to identify lumen
    - Cut with cold blade at 12 o'clock through scar tissue to corpora
    - May be helpful to leave catheter for 3-5d as stent or to have patient do CIC

### Describe the classic reconstruction of a distraction injury to the urethra.

- spatulated anast of proximal anterior urethra to apical prostatic urethra → injuries usually not long and can have 1° anast
  - proceed 4-6mo after trauma
  - endoscopy prior to placing pt in lithotomy: through meatus and through SP tract
    - r/o bladder stones
  - exaggerated lithotomy position
    - avoid pressure on lateral aspects of lower extremity and calves
    - pts hips elevated into position by raising buttocks portion of OR table
    - boots positioned to avoid stretch of common perineal nerves
  - lambda-shaped incision down to midline fusion of bulbospongiosus
  - self-retaining ring retractor
  - divide midline fusion of bulbospongiosus
  - corpus spongiosum detached from triangular ligament and cavernosa
  - bulbospongiosus detached from perineal body
  - avoid suture ligature of circumflex cavernosal arteries
  - divide triangular ligament
  - divide dorsal vein
  - introduce Haygrove staff into SP sinus and through BN to distal limits of posterior urethra
  - resect fibrosis until see normal epithelium, control w/ skin hook or stay suture
  - perform endoscopy to ensure urethrotomy at distal limit of posterior urethra
  - mobilize spongiosum to ensure tension-free anastomosis
  - proximal urethrotomy spatulated to fit 32F bougie
  - 10-12 anastomotic sutures placed (3-0 Monocryl or PDS)
  - spatulate proximal portion of anterior urethra to fit 30-32F bougie
  - place stent and complete anast, remove all clot
  - reattach corpus spongiosum to cavernosa
  - reattach bulbospongiosus to perineal body



## Chapter 110 Questions - Urethras.doc and penile surgery

- suction drain deep to closure of Colles' fascia, 2<sup>nd</sup> drain superficial to that closure
- Post-op
  - SP, urethral stent, drains
  - Ditropan, antibiotics
  - voiding trial at 3-4 weeks w/ voiding cystogram
    - ensure no extravasation, anast is widely patent
  - urine C&S, plug SP catheter
  - remove SP 5-7d later (?replace Foley at this time for few days)
  - endoscopy at 6 and 12 months

### What surgical options are available to shorten the course the sponge must travel?

- division of the triangular ligament and development of the intracurral space
- mobilization of the spongiosum from attachment to cavernosae
  - aggressive mobilization may be harmful to retrograde blood supply
- infrapubectomy
- rerouting of the spongiosum

### What is the usual cause of restenosis of the proximal bulb?

- ischemia of proximal corpus spongiosum w/ stenosis of mobilized sponge
  - usually not due to technical problems

### What is the management of vesicourethral distraction defects post-RP?

- must accurately determine length of the defect: cysto + RUG + antegrade cysto through SP tube
- abdominal and perineal reconstruction
- bladder opened and BN fibrosis resected
- anastomosis
- omentum b/w rectum and anastomosis

### What is the difference b/w a "congenital curvature of the penis" and a "chordee w/o hypospadias"?

- chordee w/o hypospadias = meatus properly located at tip of glans
- congenital curvature = associated abnormalities of ventral fascial tissue or spongiosum or both

### How can one classify congenital chordee?

- Devine and Horton 1973 classification
  - Type I: urethral meatus at tip of glans, no surrounding layers normally formed, malformation of sponge superficial to urethra
    - urethra directly beneath skin
  - Type II: dysgenetic band of fibrous tissue beneath urethra in Buck's, normal spongiosum
    - normal urethra and sponge, abnormal dartos and Buck's
  - Type III: short area of inelastic tissue in dartos layer, normal urethra, sponge, and Buck's
    - abnormal dartos only
  - Type IV: short/inelastic area of tunica albuginea of corpora, normal urethra, sponge, and fascia
    - abnormal cavernosal development only
  - Type V (congenital short urethra): normally fused urethra and sponge not long or compliant enough
- Types I-III are forms of hypospadias (chordee w/o hypospadias)
- Type IV: congenital curvature of penis
- Type V: may not exist

### What are the options for surgical correction of the adult pt w/ persistent curvature?

- lengthen the ventral aspect of the penis by making transverse incisions in ventral tunic and placing graft
  - use only if pts has chordee w/o hypospadias and if shortness of penis is an issue
- shorten dorsal aspect by elevating NVB and excising an ellipse(s) and closing the defects in watertight fashion (Nesbitt)
  - **2000 WHO consensus → majority or all pts should have plication and not grafting**

### Describe the surgical approach to the patient w/ a congenital ventral curvature.

- circumferential incision through circ scar (if present)
- deglove penis by dissecting layer immediately superficial to superficial lamina of Buck's fascia
- artificial erection
  - **do not use tourniquet** → may conceal proximal limits of curvature
- mobilize fibrous tissue and excise

## Chapter 110 Questions - Urethras.doc and penile surgery

- detach corpus spongiosum from cavernosa from glans to penoscrotal junction
- repeat artificial erection
  - occasional patient now straightened
- excise ellipses of dorsal tunica
  - elevate Buck's fascia
  - elevate NVB
  - appose edges of planned ellipses w/ Prolene and repeat artificial erection
  - excise ellipses to avoid damage to underlying erectile tissue
  - reapproximate edges w/ 4-0 PDS interrupted and watertight running 5-0 PDS
  - repeat artificial erection
- close Buck's fascia
- replace skin sleeve and reapproximate edges
- Foley, small suction drains

### What flaps can be used for total penile reconstruction?

- forearm flap: fasciocutaneous flap vascularized by the radial artery
  - elevated and transferred on the superficial fascia
    - Chang "Chinese" flap
      - ◆ skin island has 2 separate paddles:
        - ◆ ulnar "urethral" paddle
        - ◆ shaft covered by radial aspect of skin paddle
      - ◆ 2 islands separated by de-epithelialized strip
      - ◆ urethral tube rolled within the tube of skin form a tube-within-a-tube
      - ◆ tends to lead to ischemic stenosis of the urethral paddle
    - cricket bat modification
      - ◆ urethral tube extends distally
      - ◆ proximally, broader skin paddle forms shaft coverage
      - ◆ centers urethral portion over radial artery
      - ◆ useful in trauma pts
    - Biemer modification
      - ◆ centers urethral paddle over artery
      - ◆ includes portion of radius to give rigidity to penis
      - ◆ urethral paddle is a midline strip separated by 2 lateral paddles by de-epithelialized strips
    - Puckett modification
      - ◆ large island left distally, flared back over tip of the tubed flaps, creating glans
- upper lateral arm flap: if need only vascularized tissue to cover penile shaft
  - based on radial collateral artery
  - scar more easily hidden

### What are the disadvantages to the use of a forearm flap for phallic reconstruction?

- donor site deformity: scar
  - can reconstruct w/ FTSG from groin crease
- cold intolerance to donor hand
- hirsute forearm skin → hair in urethra

### What recipient vasculature can be used for flap transfer?

- deep inferior epigastric vessels
- saphenous interposition graft to superficial femoral artery

### What principles should be followed for penile reconstruction after trauma?

- urinary diversion
- debride necrotic tissue
- remove any foreign bodies
- primary reconstruction 3-6 weeks after trauma (some wait 4-6 mo)

### What flaps have been used to reconstruct the penis after trauma?

- TFL flap: for groin reconstruction
- rectus femoris flap: for inguinal and lower abdominal reconstruction
- gracilis muscle: for perineum and groin
- rectus abdominis flap

## **Chapter 110 Questions - Urethras.doc and penile surgery**

### **What is the management of the female-to-male transsexual patient?**

- complex screening and evaluation by mental health professionals, surgeons
- 1<sup>st</sup> stage: BSO+TAH, vaginectomy, urethral lengthening w/ colpocleisis  
→ divert urine x 3 weeks
- 2<sup>nd</sup> stage: penile reconstruction

### **What was the most common cause of urethral stricture disease at the beginning of the century?**

- gonococcal urethritis

### **What variables are essential to define the anatomy of a stricture?**

- length of stricture
- location of stricture
- depth of spongiofibrosis
- density of spongiofibrosis

### **What is the role of US in defining a urethral stricture?**

- transperineal US demonstrates length only  
→ cannot demonstrate extent of spongiofibrosis

### **What is the role of RUG under fluoro in defining urethral stricture?**

- difficult to assess length w/ spot film w/ fluoro
- often do not allow for visualization of the entire urethra

### **What modality of investigation allows for the best assessment of the depth of spongiofibrosis?**

- endoscopy

### **What types of strictures can be cured w/ dilation?**

- few anterior strictures cured w/ dilation
- no stricture w/ spongiofibrosis will respond long term to single dilation
- only strictures that are confined to the urethral epithelium, diaphragmatic in length, can be handled w/ dilation

### **Does VIU spread the length of stricture or decrease the success rate of eventual urethral reconstruction?**

- no evidence for either

### **Which strictures respond favourably to VIU?**

- < 1.5cm
- bulbous urethra
- associated w/ relatively superficial spongiofibrosis

### **What is the success rate for VIU?**

- 30% overall
- if adhere to above characteristics, can approach 90%

### **Can long-term cure rate be improved by addition of post-op dilation after VIU?**

- no evidence to support or contest
- may just delay recurrence

### **What are the indications for a UroLume endoprosthesis?**

- recurrent benign bulbar urethral stricture
- prostatic obstruction due to BPH

### **What stricture characteristics are suitable for UroLume placement?**

- stricture < 3cm
- distal to external sphincter, proximal to penoscrotal junction

### **What are the contraindications to UroLume placement?**

- location of stricture:  
→ meatal stricture  
→ penile urethral stricture

## **Chapter 110 Questions - Urethras.docand penile surgery**

- distal anterior urethral stricture
- bulbar urethral stricture that cannot be opened to 26F by VIU or dilation
- stricture of external sphincter
- active UTI
- urethral condition requiring transurethral manipulation w/i 8 weeks of UroLume placement
- infected suppurating strictures
- fistula at proposed prosthesis site
- urethral cancer
- perineal urethrostomy
- prior urethroplasty w/ skin
- posterior urethral distraction injury

### **What is the success rate of laser VIU vs. cold-knife?**

- some series report success of ~90%
- no overall difference b/w 2 modalities

### **What is the graft tissue of choice for anterior urethral reconstruction?**

- buccal mucosa

### **How should pts w/ indwelling Foley catheters be managed prior to urethral reconstruction?**

- d/c Foley, place SP
- leave urethra uninstrumented for > 3 months prior to reconstruction

### **When is infrapubectomy used in urethral reconstruction?**

- in posterior urethral reconstruction, when proximal urethra rostrally or posteriorly displaced
  - in bulbous urethral stricture, infrapubectomy never indicated: proximal urethra in normal position



## **Chapter 100**

### **• Basics of Laparoscopic Urologic Surgery •**

#### **What are the contraindications to laparoscopic surgery?**

- Absolute
  - uncorrectable coagulopathy
  - intestinal obstruction
  - abdominal wall infection
  - massive hemoperitoneum
  - peritonitis
  - suspected malignant ascites
- Relative
  - morbid obesity → inadequate instrument length, decreased ROM, increased pressures required, poor anatomy
  - extensive prior abdominal/pelvic surgery → adhesions
  - pelvic fibrosis
  - organomegaly → complications w/ insertion
  - ascites → risk injuring bowel from closer proximity
  - pregnancy → enter safe distance from uterus
    - LUQ is often preferred site of access
    - prolonged IAP > 15mmHg may cause decreased BP: decreased venous return from IVC compression from uterus
    - pneumoperitoneum of 10mmHg in pregnant pt
  - hernia
    - diaphragmatic hernia: CO<sub>2</sub> into pericardium
  - iliac/aortic aneurysm → enter into LUQ

#### **What modification should be considered in laparoscopy for pts w/ COPD?**

- helium as alternative insufflant → precludes problems w/ hypercarbia
  - much less soluble in blood: risk of embolus

#### **What is involved in the preop preparation for laparoscopic surgery?**

- Pre-op
  - informed consent: risk of conversion, complications
  - bowel preparation
    - retroperitoneoscopy: no bowel prep
    - transperitoneal laparoscopy: light mechanical bowel prep only → full bowel prep only if need to enter bowel or ++ risk of bowel injury
  - preparation of blood products: X+T 2u pRBC
  - preop radiologic procedures: CT, MR, angio, embolization of renal tumours
- In the OR
  - OR setup
  - pt positioning
  - prep full abdominal wall
  - NG tube: decompressed stomach to prevent injury
  - Foley: decompressed bladder to prevent injury
  - placement of OR team
  - equipment checklist: light cable, irrigation, cautery, CO<sub>2</sub> tank, white balance, gas working, veress needle working

#### **What are the advantages and disadvantages of CO<sub>2</sub> as an insufflant in laparoscopy?**

- Advantages
  - does not support combustion
  - very soluble in blood: decreased risk of embolus
  - prolonged post-op distension does not occur due to quick absorption
- Disadvantages

## **Chapter 100 Questions - Lap surgery.doc**

- risk of hypercarbia, hypercapnia, associated cardiac arrhythmias
- CO<sub>2</sub> stimulates the sympathetic nervous system: increased HR, cardiac contractility, and vascular resistance

### **What are the different techniques for obtaining a pneumoperitoneum?**

- Closed
  - Veress needle
    - head of bed lowered 10-20 degrees, 12mm incision in skin
    - tissues spread w/ Kelly, anterior fascia secured w/ towel clips
    - needle passed towards the pelvis, away from the bowels
    - 2 pts of resistance: abdominal wall fascia and peritoneum
    - start insufflation at 1 L/min
- Open: Hasson-style cannula
- Endopath: transparent trocar
- gasless open technique: mechanical device lifts abdominal wall

### **What tests can be performed to ensure that a Veress needle has properly entered the peritoneum?**

- Aspiration/Irrigation/Aspiration
  - Veress needle aspirated to check for blood/stool
  - NS injected into abdominal cavity: should be no resistance
  - plunger withdrawn: no fluid should return
- Hanging Drop test: drop of NS placed into Veress hub → should fall into peritoneal cavity
- Advancement test: should be able to advance needle 1-2cm w/o resistance

### **What are the advantages to using the umbilicus as the initial port site?**

- abdominal wall is thinnest
- no major blood vessels
- postop cosmesis is excellent

### **Why should one never use a metal trocar in conjunction w/ an outer plastic retaining ring?**

- stray current can no longer be harmlessly dissipated through the metal cannula to the surrounding peritrocar abdominal wall
- can be passed to bowel

### **How does the harmonic scalpel work?**

- electrical energy is produced by a power-supply generator
- transformed into mechanical vibration within a handpiece that contains piezo-electric crystals
- mechanical vibration transferred to scissors or a hook blade
- no risk of thermal damage or charring: working temperature < 80°C

### **How does the Argon beam coagulator work?**

- noncontact form of electrocoagulation
- electrical current from a monopolar electrosurgical generator conducted to the tissue via an ionized argon gas stream
- gas stream blows away blood from the tissue, resulting in better visualization and better fulguration
- used mostly during partial nephrectomy

### **What considerations are important in port removal for laparoscopy?**

- operative site must be inspected
  - venous bleeding w/ decreased pneumoperitoneum
  - surgical site irrigated w/ antibiotic solution
- remove lap ports under visual control to prevent herniation of intra-abdominal contents
- fascia closed w/ 2-0 Vicryl

### **What methods are available for port site closure?**

- retract skin and grasp fascia w/ Kocher → close
- Foley insertion into port site → pulls abdominal wall upwards
- straight, closed, Lowsley retractor
- Carter-Thomason needlepoint suture passer → metal cone w/ passages 180 degrees apart
- Maciol suture needle set
- eXit disposable puncture closure device
- disposable Endo Close suture carrier

## Chapter 100 Questions - Lap surgery.doc

- disposable Tahoe surgical instrument ligature
- angiocatheter technique

### What alternative gases can be used in laparoscopy other than CO<sub>2</sub>?

- Nitrous oxide
  - less irritating to peritoneum
  - fewer acid-base changes compared w/ CO<sub>2</sub>
  - reduces CO and increases MAP, HR, and CVP
  - **risk of combustion: only used w/ no electrosurgical instruments**
- Helium
  - inert and noncombustible
  - used for pts w/ COPD in whom hypercarbia would be poorly tolerated
  - **if hypercarbia develops during laparoscopy, switch to helium**
  - associated w/ higher risk of gas embolus → lower blood solubility
  - more expensive than NO or CO<sub>2</sub>
- room air, O<sub>2</sub> → serious side effects
- noble gases → not used due to cost

### What are the physiologic effects of pneumoperitoneum?

- CVS effects
  - Venous flow
    - venous return low if atrial pressures are low: due to increased IVC compression → generally lowered
    - venous return high if atrial pressures are high: IVC resists compression
  - Cardiac arrhythmias
    - tachycardia and ventricular extrasystoles: due to hypercapnia
    - bradyarrhythmia: due to vagal stimulation from peritoneal irritation
  - unreliability of CVP readings: increased IAP may artificially raise CVP readings
- Respiratory effects: pressure-mediated vs. non-pressure-related effects
  - PEEP needed to keep constant tidal volume increases w/ increased IAP
  - head-down position adversely affects respiration: elevates diaphragm, decreases vital capacity, pulmonary edema
  - ET CO<sub>2</sub> increases w/ increasing IAP
  - pCO<sub>2</sub> increases w/ increasing IAP
  - arterial pH decreases w/ increasing IAP
- Renal and other visceral effects
  - oliguria: from decreased RBF and direct renal parenchymal compression
    - GFR decreases w/ increasing IAP
    - cortical BF decreases while medullary BF increases (if < 20mmHg)
  - decreased mesenteric blood flow and decreased intestinal motility
- Acid-Base metabolic effects
  - hypercarbia and respiratory acidosis from transperitoneal absorption of CO<sub>2</sub>: dangerous in pts w/ COPD
- Hemodynamic effects
  - due to positioning
    - CO unchanged w/ IAP < 15mmHg
    - CO decreases w/ IAP > 20mmHg due to decreased venous return
    - increased venous return (and CO) in head down position
  - due to hypercarbia
    - CVS stimulation if IAP 5-20mmHg: decreased PVR, increased HR, enhanced contractility
  - MAP and SVR increase w/ insufflation (MAP increases w/ IAP up to 20mmHg)
- Hormonal and Metabolic effects
  - β-endorphin, cortisol, PRL, epi, NE, dopamine increase during laparoscopy
- Immunologic effects
  - inflammatory response mediators (CRP, IL-6) and other markers (CD3, CD4, CD8, CD16) suggest laparoscopy results in less immunosuppression than open procedures

### What are the reasons for choosing various pneumoperitoneum pressures?

- 10mmHg: absence of oliguria
- 15mmHg: most common
- 20mmHg: increased insufflant volume and decreased venous bleeding

### What are the complications associated w/ laparoscopic procedures?

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- Related to obtaining pneumoperitoneum
  - malfunction of equipment
  - complications associated w/ closed access
    - preperitoneal placement of needle
    - vascular injuries → make sure to direct needle toward the hollow of the pelvis
    - visceral injuries → if aspirate blood, urine, or bowel contents: remove needle, reintroduce at different site
  - complications associated w/ insufflation and pneumoperitoneum
    - bowel insufflation
    - gas embolism
    - barotrauma: prolonged elevated pressures > 15mmHg
    - subcutaneous emphysema → usually due to poor placement of Veress needle or leakage around ports
    - pneumomediastinum and pneumopericardium: usually no sx, but may impair cardiac fn
    - pneumothorax
  - complications associated w/ open access
    - injury to underlying viscera
  - complications related to initial placement of "blind" trocar
    - bowel injury: if missed, leads to peritonitis and death
    - vascular injury: usually aorta or common iliac
    - GU injury
- Related to placement of secondary trocars
  - position related problems: "crossing swords", "striking handles", and "rollover" → ports too close to each other
  - injury to abdominal wall vessels (inferior epigastric vessels) → prevent by placing all port sites > 6cm off midline
- Related to surgical procedure
  - bowel injury
    - electrosurgical
    - mechanical
  - vascular injury: IVC, renal vein, renal artery, aorta
  - GU tract injury
    - bladder
    - ureter
  - nerve injury
- Related to exiting the abdomen
  - bowel entrapment
  - bleeding at sheath site
  - acute hydrocele: due to patent processus vaginalis, usually resolves
  - scrotal and abdominal ecchymosis
- Postop complications
  - pain
  - incisional hernia: close all port sites 10mm or larger (5mm in kids) w/ 2-0 SAS
  - subcutaneous emphysema
  - DVT/PE
  - wound infection
- Related to GA unique to laparoscopy
  - cardiac arrhythmias and cardiac arrest: usually sinus tachycardia, or bradyarrhythmias
  - changes in BP
    - hypertension: due to inadequate GA, elevated IAP, hypercarbia, hypoxia
    - hypotension: due to hypoxia, pneumothorax, pneumomediastinum, gas embolus, hemorrhage
  - aspiration of gastric contents: increased risk if hiatal hernia, obesity, DM w/ gastroparesis, or gastric outlet obstruction
  - hypothermia: due to cold CO<sub>2</sub> insufflant

### What are the signs of preperitoneal needle placement?

- unequal distension of the abdomen
- fat seen after laparoscope placement

### What are the signs of bowel insufflation?

- asymmetrical abdominal distension
- flatus
- insufflation of <2L before high pressures reached



## **Chapter 100 Questions - Lap surgery.doc**

### **What are the signs of intravascular insufflation (gas embolus)?**

- acute cardiovascular collapse
- dysrhythmia, tachycardia
- cyanosis
- pulmonary edema
- abrupt increase in ET $\text{CO}_2$
- decline in  $\text{O}_2$  saturation then marked decrease in ET $\text{CO}_2$
- "millwheel" precordial murmur

### **How does one treat intravascular insufflation (gas embolism)?**

- immediate cessation of insufflation
- prompt desufflation of peritoneal cavity
- turn pt into LLD position to decrease R ventricular outflow resistance
- hyperventilate pt w/ 100%  $\text{O}_2$
- hyperbaric oxygen
- advancement of central line into R heart to aspirate gas: rarely helpful

### **What are the signs of barotrauma?**

- hypotension: compression of IVC  $\rightarrow$  acute drop in venous return  $\rightarrow$  decreased CO
- pneumothorax
- pneumomediastinum
- increase in ventilation pressures

### **How can one prevent pneumomediastinum or pneumopericardium during laparoscopy?**

- keep IAP < 15mmHg
- make sure all port sites are tight around cannula
- make sure all cannulas are well seated in peritoneum

### **What are the signs of pneumothorax during laparoscopy?**

- subcutaneous emphysema: esp in head and neck
- hypotension
- decreased breath sounds
- increased ventilatory pressures
  - $\rightarrow$  tension pneumothorax

### **How does one treat a bowel injury during laparoscopy?**

- one-wall
  - $\rightarrow$  leave trocar in place and pass 2<sup>nd</sup> trocar using open technique
  - $\rightarrow$  open and repair bowel vs. close laparoscopically using 3<sup>rd</sup> port
  - $\rightarrow$  irrigate peritoneum w/ 4-5L NS w/ antibiotic solution
  - $\rightarrow$  place pt on triple-coverage antibiotics
- two-wall
  - $\rightarrow$  open and repair bowel
  - $\rightarrow$  irrigate peritoneum w/ 4-5L NS w/ antibiotic solution
  - $\rightarrow$  place pt on triple-coverage antibiotics

### **What are the signs of vascular injury during trocar placement?**

- sudden hypotension
- tachycardia
- pulsatile (arterial) vs. non-pulsatile (venous) profuse return of blood from trocar
- mesenteric hematoma
- blood rapidly accumulating in peritoneum
- blood accumulating in retroperitoneum

### **How does one treat a vascular injury during trocar placement?**

- call vascular or trauma surgeon
- leave trocar in place if blood coming through trocar
- emergency laparotomy
- trocar followed to pt of entry into vessel

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### **How can one treat an injury to the inferior epigastrics during trocar placement?**

- pass electrocautery scissors through 2<sup>nd</sup> port → visualize bleeding and electrocoagulate
- suture area of hemorrhage
  - insert straight Keith needle w/ 2-0 absorbable suture from outside abdomen at one side, grasp w/ lap forceps and pass through other side, tie over gauze bolster
- port closure device: Carter-Thomason

### **What are the mechanisms by which electrosurgically induced thermal injury to bowel may occur during laparoscopy?**

- inappropriate direct activation → accident: "Whoops!"
- coupling to 2<sup>nd</sup> instrument
- capacitive coupling
  - surrounding charge (intrinsic to all monopolar electrodes) not allowed to conduct back to and disperse via abdominal wall
  - may develop when metal cannula anchored to skin via plastic grip
  - electrical field builds up around activated instrument and cannot be conducted through to abdominal wall
  - electrical charge can travel to other tissues
- insulation failure
  - current can escape along the shaft of the instrument

### **How can one treat a vascular injury during laparoscopy?**

- increase pneumoperitoneum to 25mmHg → slows venous bleeding
- irrigate/aspirate blood to identify bleeding site
- introduce sponge into abdomen
- identify and tamponade bleeding
- patch/glue
- vascular consult
- convert to open
- repair laparoscopically w/ lap Satinsky or w/ Endostitch
- arterial: much harder to deal with laparoscopically

### **What factors predispose pts to GU injury during laparoscopy?**

- reported most extensively w/ gyne procedure
- bladder or pelvic anomalies
- acute or chronic inflammation
- prior pelvic/bladder surgery
- endometriosis
- malignant infiltration
- bladder diverticulae
- amyloidosis
- hx of radiation

### **What are the signs of GU injury during laparoscopy?**

- Bladder
  - Intraoperative
    - blood/gas in Foley bag
    - clear fluid welling up in pelvis
  - Postoperative
    - oliguria
    - urinary ascites
    - hyponatremia, hyperkalemia, increased serum Cr
- Ureter
  - not usually noticed intraoperatively
  - Postoperative
    - abdominal/flank pain 2-3 days postop
    - fever
    - peritonitis
    - increased WBC

### **What is the etiology of nerve injury during laparoscopy?**

- pt positioning and duration of procedure → usually brachial plexus

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- abduction of arm > 90 degrees
- extreme outward rotation of head of humerus
- compression damage w/ shoulder braces used in Trendelenburg
- direct mechanical injury
- electrosurgical injury
  - obturator nerve during PLND
  - genitofemoral during nephrectomy/NUU

### **How does one treat a nerve injury due to laparoscopy?**

- Intraoperative
  - neurosurgical consult
  - repair nerve w/ 6-0 suture
- Postoperative
  - neurology consult
  - PT consult

### **How can one prevent a nerve injury during laparoscopy?**

- pronate arms if at pts side to protect brachial plexus
- pad all bony prominences → check each time table is moved
- do not use shoulder braces
- avoid extreme abduction of hips

### **How does one treat bowel entrapment during desufflation of the abdomen?**

- re-establish pneumoperitoneum
- visualize entrapped bowel, pull into peritoneum

### **What are the causes of post-op pain after laparoscopy?**

- herniation of bowel
- infection
- rectus sheath hematoma
- palpation of knot
- release of noxious material during OR: cyst fluid
- bowel injury
- CO<sub>2</sub> irritation of diaphragm

### **What factors common to laparoscopy lead to development of arrhythmias during laparoscopy?**

- CO<sub>2</sub> insufflation
- hypercapnia
- increased vagal tone due to traction on pelvic or peritoneal structures → can preoperatively medicate w/ atropine to try to prevent
- Trendelenburg position
- anaesthesia: halothane
- preop pt anxiety
- endobronchial intubation
- gas embolus

### **What are the clinical effects of hypothermia?**

- increased bleeding tendency: poor platelet fn, reduced activity of coag factors, enhanced fibrinolysis
- increased adrenergic response w/ vasoconstriction and increased arterial BP
- prolonged recovery time from increased blood gas solubility and decreased MAC of anaesthetics
- 2-3X increase in incidence of early postop MI
- impaired wound healing and increased susceptibility to wound infection

### **Describe the technique of retroperitoneoscopy.**

- Pt positioning
  - full flank position
  - access in space b/w 12<sup>th</sup> rib superiorly, iliac crest inferiorly, lateral border of paraspinous muscles posterolaterally, and lateral peritoneal reflection anteromedially
  - elevate kidney rest and flex OR table
- Access

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- Open: safer, quicker, more precise
  - 15mm transverse incision in midaxillary line below tip of 12<sup>th</sup> rib
  - posterior layer of lumbodorsal fascia incised
  - retroperitoneal space entered by making incision in anterior thoracolumbar dorsal fascia w/ electrocautery blade or bluntly piercing the fascia w/ finger or snap
  - finger palpation of psoas and Gerota's to confirm proper positioning
  - index finger to create a space
- Closed
  - place Veress needle in inferior lumbar triangle (Petit's triangle)
  - CO<sub>2</sub> insufflation creates a small pneumoretroperitoneum
  - blind insertion of primary trocar
  - bluntly create a space w/ laparoscope
- Developing the retroperitoneal space
  - balloon dilation
  - self-styled dilators
- Port placement
  - balloon dilator replaced w/ 10mm port
  - posterior 2<sup>nd</sup> port placed at lateral border of paraspinal muscles along inferior border of 12<sup>th</sup> rib
  - anterior 3<sup>rd</sup> port placed near anterior axillary line, 2-3 fingerbreadths above ASIS
  - secondary ports should be inserted as far apart as possible

### What are the landmarks one should observe after balloon dilation for retroperitoneoscopy?

- psoas muscle
- Gerota's
- lateral peritoneal reflection
- ureter
- fat-covered pulsations of the renal artery
- aortic pulsations on L
- undulating pulsations of IVC on R

### What are the boundaries of Petit's (inferior lumbar) triangle?

- iliac crest (below)
- external oblique (laterally)
- latissimus dorsi (medially)

### What are the physiologic effects of retroperitoneoscopy?

- Respiratory
  - increased pCO<sub>2</sub>: variable amounts of gas absorption, increases during 1st 30-60min, then plateaus
  - rise in ETCO<sub>2</sub>
  - "false" pneumothorax: due to CO<sub>2</sub> gas tracking cephalad along denuded psoas into extrapleural space
- CVS
  - minimal compared to transperitoneal laparoscopy: decreased SV, increased dBP/MAP/HR

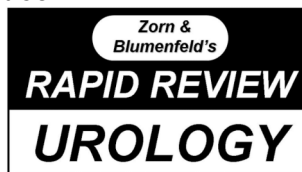
### What are the advantages and disadvantages to retroperitoneoscopy?

- Disadvantages
  - steep learning curve
  - limited space available
  - difficult to entrap specimens in smaller space
- Advantages
  - minimal risks of inadvertent bowel injury
  - less ileus
  - decreased shoulder-tip pain
  - lower incidence of trocar site hernias
  - previous transperitoneal procedure does not prevent this procedure
  - rapid and direct access to renal hilum

### What are the contraindications to retroperitoneoscopy?

- hx of prior open retroperitoneal surgery
  - prior percutaneous renal procedures is not a contraindication





## **Chapter 102**

### **• Surgery of the Kidney •**

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#### **Describe the anatomic relationships of the kidneys.**

- posteriorly: lie on psoas major and quadratus lumborum
- upper pole in contact w/ diaphragm
- anterior medial surface of R kidney in contact w/ R adrenal
- 2<sup>nd</sup> portion of duodenum covers R renal hilum
- liver overlies upper 2/3 of R kidney
- hepatic flexure overlies lower 1/3 of R kidney

#### **How often due multiple renal arteries occur?**

- unilateral 23%, bilateral 10%

#### **What is involved in the preop preparation before renal surgery?**

- Hx
  - CVS, respiratory disease: vent capacity and venous return diminished in flank position → choose non-flank position
  - bleeding tendencies
  - EtOH, ASA
- Px
- Ix
  - ECG, CXR
  - CBC, coags, Cr, differential renal fn
  - PFT, ABG
  - IVP, cysto, retrograde, ureteroscopy, MR, angio, CTA
- percutaneous embolization for large malignancies: EtOH, coils

#### **What is the change in GFR that is ultimately reached after nephrectomy?**

- 75% of normal value

#### **What is the renal response to warm ischaemia?**

- kidney very susceptible to warm ischaemia
- immediately after renal artery occlusion, energy-rich ATP within the kidney breaks down into AMP to provide energy for maintenance of structural and functional cellular integrity
- warm ischemia up to 30 minutes is tolerated
  - after 30 min, generally significant, immediate functional loss
- renal ischemia most damaging to PCT → necrosis and regeneration
  - glomeruli and blood vessels are spared
- solitary kidney more resistant
- **intermittent clamping of renal artery more damaging than continuous**
- clamping of artery and vein more damaging than clamping artery alone → prevents retrograde perfusion
- manual renal compression more damaging than renal artery occlusion

#### **How can one prevent ischemic renal damage?**

- hydration: intraop and preop
- prevent hypotension
- avoid unnecessary manipulation/traction on renal artery
- intraop mannitol: 5-15 min prior to arterial occlusion
- local hypothermia
  - surface cooling vs. perfusion

#### **What surgical approaches to the kidney are available?**

- open
  - flank approach

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- above 11<sup>th</sup> or 12<sup>th</sup> rib
- subcostal incision
- dorsal lumbotomy
- abdominal approach
- thoracoabdominal approach
- laparoscopic

### What are the advantages and disadvantages to each surgical approach to the kidney?

- flank approach
  - useful in obese pt
  - extraperitoneal: minimal disturbance to other viscera
  - avoids contamination of peritoneum
  - drainage of perirenal space readily established
  - exposure of renal pedicle not as good as with transperitoneal approach
  - unsuitable for pt w/ scoliosis or cardio/resp problems:
    - decreased venous return from IVC compression and dependent position of legs
    - limits aeration of lung on dependent side
- subcostal flank
  - indicated for surgery on lower pole or upper ureter, insertion of nephrostomy tube, drainage of perinephric abscess
  - difficult to access pedicle or renal pelvis in adults
- dorsal lumbotomy
  - useful for removal of small kidney, bilateral nephrectomy in ESRD, open renal bx, pyeloplasty, pyelolithotomy, upper ureterolithotomy
  - no muscles are transected
  - rapid
  - strong wound closure w/ less postop pain
  - prevents flank bulge
  - no resection of rib needed
  - dissection of fresh tissue planes if previous operations
  - limited access to kidney and renal vessels: bleeding, stone migration
- abdominal approaches
  - exposure in renal pedicle is excellent
  - longer post-op ileus
  - complication of intra-abdominal adhesions: bowel obstruction
- thoracoabdominal approach
  - used for large tumours of upper pole
  - good to use on R side, where liver and venous drainage into IVC can limit exposure
  - less needed on L side: spleen and pancreas mobile

### How does one determine the choice of rib for the flank approach?

- depends on kidney position and upper/lower pole
- draw a horizontal line on IVP from renal hilum to most lateral rib it intersects

### Describe the technique of flank approach to the kidney.

- Positioning
  - lateral position
  - tip of 12<sup>th</sup> rib over kidney rest
  - bottom leg flexed to 90°, top leg straight to maintain stability
  - pillow b/w legs, sponge under axilla
  - pt secured w/ tape
  - upper arm secured to Mayo stand
  - table flexed
    - assess BP after flexion: decreased venous return may cause hypotension
- Incision
  - flank incision directly over appropriate rib
  - from lateral border of sacrospinalis
  - external oblique and latissimus dorsi and serratus inferior posterior are divided
  - periosteum of rib incised w/ scalpel
  - periosteal elevator used to reflect periosteum off rib
  - proximal end of rib may be transected

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- pleura reflected upwards by sharply dividing the fascial attachments to the diaphragm
- incise lumbar fascia and insert 2 fingers into paranephric space to push peritoneum forwards
- lateral peritoneal reflection peeled off undersurface of the anterior abdominal wall and transversalis fascia
- internal oblique muscles divided, transversus muscle split
- incise Gerota's fascia posteriorly
  - avoid injury to iliohypogastric and ilioinguinal nerves as they come from behind lateral border of psoas
- Closure
  - avoid inclusion of intercostal nerves or branches during closure
  - injection of Marcaine 0.5%

### Describe the technique of the subcostal approach to the kidney.

- start at lateral border of sacrospinalis where it crosses inferior edge of 12<sup>th</sup> rib, to below lower border of last rib onto anterior abdominal wall
- medial end of incision curved downwards as it passes midaxillary line to avoid subcostal nerve
- latissimus dorsi divided in posterior portion of wound
- serratus inferior posterior divided in posterior portion of wound
- external oblique is divided anteriorly
- internal oblique is divided
- transversus is separated bluntly
- division of costotransverse ligament

### Describe the technique of the dorsal lumbotomy.

- pt in prone position: may be lateral position if unilateral renal OR
- pt supported over sternum and pubis
- vertical lumbar incision along lateral margin of sacrospinalis
- begins at upper margin of 12<sup>th</sup> rib, follows gentle curve to iliac crest inferiorly
- lateral to sacrospinalis and quadratus lumborum: retracted medially
- transverse fascia incised to expose kidney w/i Gerota's
- costovertebral ligamentous attachments of 12<sup>th</sup> rib divided for additional exposure

### Describe the technique of the abdominal approach to the kidney.

- Choice of incision
  - transverse: used in pts w/ wide subcostal angle, exploration of renal mass lesions, better access to lateral/superior pole, can be extended as a Chevron
  - vertical: easy to close, used in pt w/ narrow subcostal angle, preferred in pts w/ renal injury
- Positioning
  - supine position w/ rolled sheet under upper lumbar spine
- Incision (subcostal)
  - start 1-2cm below costal margin
  - extends in gentle curve across midline, ending at midpoint of opposite rectus
  - incise to anterior fascia, which is divided in direction of incision
  - latissimus may be divided
  - external oblique is divided
  - rectus, internal oblique, and transversus are divided along w/ posterior rectus sheath
  - peritoneal cavity entered in midline
  - divide ligamentum teres
- Incision (extraperitoneal subcostal)
  - useful if previous intra-abdominal procedure or need for PD
  - semioblique position
  - muscle layers divided as per subcostal, peritoneum not entered
  - peritoneum mobilized intact from undersurface of lateral musculature and rectus sheath, retracted medially
- Incision (paramedian)
  - closure of 2 layers of rectus sheath: more secure
  - 3cm lateral to midline

### Describe the technique of the thoracoabdominal approach to the kidney.

- Position
  - semioblique
  - rolled sheet underneath the flank
  - lower leg flexed, upper one extended, w/ pillow b/w



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- Incision
  - start in 8<sup>th</sup> or 9<sup>th</sup> intercostal space near angle of rib, carried across costal margin to midpoint of opposite rectus
  - latissimus, external oblique, rectus, and intercostal muscles divided
  - costal cartilage b/w tips of adjacent ribs is divided
  - pleura in posterior portion of incision is opened
  - diaphragmatic incision started 2cm inside its attachment to chest wall
  - divide diaphragm in circumferential manner from anterior to posterior: avoids damage to phrenic nerve
  - internal oblique and transverse abdominal muscles are divided
  - peritoneal cavity entered
  - colon and duodenum mobilized medially
  - liver retracted upwards to expose kidney
- Closure
  - diaphragm repaired w/ interrupted 2-0 silk mattress
  - chest wall reapproximated w/ 0 Vicryl sutures around ribs and above
  - avoid neurovascular bundle
  - 20F chest tube
  - post-op CXR

### What are the indications for simple nephrectomy?

- irreversibly damaged kidney due to:
  - infection, obstruction, stones, severe trauma
- renovascular htn due to:
  - noncorrectable RAS
  - severe unilateral parenchymal damage (from nephrosclerosis, pyelo, VUR, dysplasia)
- donor transplant

### What are the potential approaches for simple nephrectomy and their indications?

- extraperitoneal flank
  - used when kidney chronically infected, pt obese, or multiple previous abdominal ORs
- subcapsular
  - used if severe perirenal adhesions/inflammation b/w kidney and surrounding structures
- transperitoneal
  - pts who cannot tolerate flank position, ESRD
  - ESRD w/ bilateral nephrectomy (PCKD)
  - traumatic renal injury
  - multiple previous flank procedures
- dorsal lumbotomy
  - small end-stage kidneys

### Describe the technique of simple nephrectomy.

- Flank approach
  - enter perinephric space as previous
  - incise Gerota's on lateral aspect of kidney: avoid injury to overlying peritoneum
  - mobilize kidney by blunt dissection
  - L side: reflect panc and duodenum
  - identify ureter
  - pull kidney down, dissect free upper pole
  - separate adrenal from upper pole
  - pull kidney laterally to identify renal artery and vein
  - ligate artery, then vein w/ 2-0 silk and divide
  - divide ureter and ligate w/ 2-0 chromic
- Subcapsular technique
  - renal capsule identified and longitudinal incision made
  - plane developed b/w parenchyma and capsule
  - renal parenchyma retracted laterally to expose major vessels
  - vascular branches ligated and transected
  - ureter divided and transected

### What are the indications for radical nephrectomy?

- localized RCC

## **Chapter 102 Questions - Kidney surgery.doc**

- metastatic RCC
  - for local control of sx
  - w/ resection of solitary met
  - for entry into clinical trial

### **What are the principles of radical nephrectomy?**

- early ligation of renal artery and vein
- removal of kidney outside Gerota's
- removal of ipsilateral adrenal
- complete regional lymphadenectomy from crus to aortic bifurcation → **controversial**

### **Describe the technique of radical nephrectomy.**

- Pre-op evaluation
  - metastatic evaluation: CXR, CT, bone scan (if bone pain or increased ALP)
- Procedure
  - incision: dependent on disease
  - reflect colon and duodenum if transperitoneal
  - dissect out renal pedicle
  - mobilize renal vein w/ division of gonadal, adrenal, and lumbar tributaries
  - renal artery and vein ligated w/ 2-0 silk and divided
  - kidney mobilized outside Gerota's
  - ureter ligated and divided

### **What is the incidence of IVC tumour thrombus in RCC?**

- 4-10%

### **What sx can suggest IVC tumour thrombus?**

- lower extremity edema
- varicocele
- dilated superficial abdominal veins
- proteinuria
- PE
- R atrial mass
- nonfunction of affected kidney

### **What are the sites of predictable bleeding during radical nephrectomy?**

- lumbar veins entering posterolateral IVC at each vertebral level: ligate and divide w/ 3-0 silk
- R gonadal vein entering anterolateral IVC
- lumbar veins entering posterior L renal vein or posterior IVC close to R renal vein entry
- R adrenal vein entering IVC

### **How can one manage retroperitoneal hemorrhage during radical nephrectomy?**

- direct pressure on bleeding sites
  - additional exposure, improve lighting, additional suckers and retractors
- laceration of anterior or lateral IVC: apply series of Allis clamps and oversew w/ running 5-0 Prolene
- avulsion of lumbar vein: roll IVC medially w/ compression above and below, grasp hole w/ Allis
- bleeding from retracted proximal end of lumbar: grasp vein w/ snap and bring into view to ligate
  - figure-of-eight 2-0 silk over muscle overlying vein
- bleeding from L lumbar entering renal vein: mobilize IVC, place Satinsky on entry of renal vein and distal bulldog

### **What are the different levels of IVC tumour thrombus involvement?**

- renal
- infrahepatic
- intrahepatic
- suprahepatic

### **Describe the technique of radical nephrectomy w/ infrahepatic IVC thrombus.**

- bilateral subcostal or thoracoabdominal incision
- reflect colon medially
- ligate renal artery and ureter → kidney attached only by renal vein

## Chapter 102 Questions - Kidney surgery.doc

- avoid unnecessary manipulation of renal vein and IVC
- IVC dissected from surrounding structures above and below renal vein
- contralateral renal vein mobilized
- divide perforating veins to caudate lobe of liver to allow separation of caudate from IVC
  - can gain 2-3cm of additional IVC
- infrarenal IVC occluded below thrombus w/ Satinsky, opposite renal vein secured w/ bulldog
- suprarenal IVC secured w/ curved Satinsky
- anterior renal vein incised over tumour thrombus, incision continued posteriorly w/ scissors
- gentle downward traction to extract tumour thrombus
- suprarenal clamp released momentarily while anaesthetist applies +ve pressure
  - flushes small bits of tumour out of IVC
- repair IVC w/ 5-0 Prolene

### By how much can one narrow the IVC lumen w/o adversely affecting IVC patency?

- 50%

### How can one manage infrahepatic IVC invasion by RCC?

- direct IVC invasion only at site of renal vein entrance: resect portion of IVC wall
- extensive direct growth of tumour into wall
  - R sided tumours: may resect entire IVC below liver
    - ligate L renal vein distal to gonadal and adrenal tributaries
  - L sided tumours: cannot resect IVC → no collateral venous circulation from R kidney
    - maintain tumour free strip of IVC + pericardial patch
    - R kidney autotransplantation to pelvis
    - saphenous vein graft from R renal vein stump to splenic/IMV/portal vein

### What are the techniques for maintaining vascular control in suprahepatic IVC thrombus?

- temporary occlusion of suprahepatic intrapericardial portion of IVC
  - requires temporary occlusion of porta hepatis and SMA to reduce hepatic venous congestion
  - safely tolerated for only 20 minutes
  - not applicable in R atrial tumour thrombus
- cardiopulmonary bypass w/ hypothermic arrest
- temporary venovenous bypass w/ caval-atrial shunt
  - intrapericardial IVC, infrarenal IVC, opposite renal vein temporarily occluded

### Describe the technique of radical nephrectomy w/ intrahepatic or suprahepatic IVC thrombus.

- bilateral subcostal or thoracoabdominal incision
- reflect colon medially
- ligate renal artery and ureter → kidney attached only by renal vein
  - if L RCC, transpose kidney through mesenteric window
- IVC dissected from surrounding structures below renal vein
- contralateral renal vein mobilized
- bypass and hypothermic arrest → can maintain for 40min w/ low risk of stroke
  - median sternotomy
  - pt heparinized
  - ascending aortic and R atrial venous cannulae placed, bypass initiated
  - when heart fibrillates, aorta is clamped and crystalloid cardioplegic solution infused
  - reduce arterial inflow solution to 10°C
  - pack head and abdomen in ice
  - flow through perfusion machine is stopped, and 95% of blood drained into pump w/o flow into any organ
- removal of tumour thrombus
  - incision in IVC at entrance of renal vein
  - atrium opened at same time
  - tumour thrombus removed intact w/ kidney
  - entire IVC inspected visually in bloodless field
- IVC repaired w/ running 5-0 Prolene
- R atrium closed
- rewarming over 20-45min to core temp of 37°C
- stop bypass
- decannulation

## Chapter 102 Questions - Kidney surgery.doc

- protamine given to reverse heparin

### What are the complications of radical nephrectomy?

- occur in approximately 20%
- mortality rate of 2%
  - systemic complications
    - MI, stroke, CHF, DVT/PE, atelectasis, pneumonia, thrombophlebitis
  - GI injury
    - bowel injury
    - liver laceration
    - splenic injury
    - pancreatic tail injury
    - pancreatic fistula → CT shows fluid collection, send for pH and amylase: tx w/ drainage, TPN
    - ileus
  - bleeding
  - infection
  - lymphocele
  - Pulmonary
    - pneumothorax
    - pleural injury
    - lung parenchymal injury
  - temporary renal insufficiency
  - incisional hernia
  - flank bulge

### What are the indications for chest tube after pleural injury during nephrectomy?

- pneumothorax > 10%
- tension pneumothorax
- symptomatic pneumothorax

### What are the indications for partial nephrectomy?

- Malignancy
  - when radical nephrectomy would render pt anephric w/ immediate need for dialysis
    - bilateral RCC
    - RCC involving solitary kidney (congenital solitary, functional solitary, or fusion anomaly [horseshoe])
  - unilateral RCC w/ potential for future renal disease
    - local: stones, chronic pyelo, VUR, RAS
    - systemic: DM, htn, nephrosclerosis or other GN
  - predisposition for recurrence: VHL, TS
  - relative: unilateral RCC w/ single small RCC < 4cm, N0M0, and able to get -ve margin
  - renal pelvis TCC or Wilms' tumour w/ need for preservation of renal parenchyma
- Benign disease
  - Congenital
    - non-functioning pole from any cause: duplex, ureterocele, ectopia, VUR
      - ◆ segmental parenchymal disease w/ impaired drainage
    - hydro w/ parenchymal atrophy or atrophic pyelo in duplex kidney
      - ◆ obstructed or nonfunctioning duplex segment
    - RVH due to scarring
    - RAA
    - AVM
    - AV fistula
  - Infection
    - TB
    - abscess
  - Trauma w/ irreversible damage to part of kidney
  - Neoplasm: benign
    - AML
    - oncocytoma
    - reninoma
  - Vascular: noncorrectable segmental RAS

## Chapter 102 Questions - Kidney surgery.doc

- Stone w/ lower pole calyx obstruction w/ impaired drainage
- Calyceal diverticulum complicated by infection or stones or both

### What is the risk of postop local RCC recurrence in partial nephrectomy?

- 4-6%

### How does one manage bilateral synchronous RCCs?

- large tumours
  - approach kidney more amenable to partial first
  - 1 month later, perform partial or radical nephrectomy on more difficult kidney
- small tumours
  - bilateral simultaneous partial nephrectomy

### What are the possible techniques for partial nephrectomy?

- simple enucleation
  - high risk of leaving residual malignancy
  - use occasionally in VHL pts w/ multiple low stage encapsulated tumours bilaterally
- wedge resection
- polar segmental nephrectomy
  - isolate and ligate segmental apical or basilar arterial branch while allowing unrepaired perfusion to rest of kidney
  - methylene blue can be injected into segmental branch to delineate segment
- transverse resection (heminephrectomy)
  - used to remove large tumours that extensively involve upper or lower portion of kidney
  - use surface hypothermia after temporary occlusion of renal artery
- extracorporeal partial nephrectomy w/ renal autotransplantation
  - flush kidney immediately after division of vessels w/ 500cc chilled solution, submerge in ice
  - leave ureter attached if possible to preserve distal blood supply
  - autotransplant into iliac fossa

### Describe the technique of partial nephrectomy (wedge resection).

- Preoperatively
  - r/o locally extensive or metastatic disease
  - renal angio or CTA or CT
  - hydration and mannitol
- Incision: extraperitoneal flank incision → 11<sup>th</sup> or 12<sup>th</sup> rib
- kidney mobilized within Gerota's
  - perirenal fat around tumour left intact
- in situ renal hypothermia → if renal circulation temporarily interrupted
  - surface cooling of kidney w/ ice slush: good for 3hrs
  - don't do partial until 15min after slush added
  - IV injection w/ mannitol
- inspect kidney for multifocality
- partial nephrectomy
  - parenchyma around tumour divided w/ sharp and blunt dissection
    - tumour removed w/ several-mm margin of normal renal parenchyma
  - identify vessels as parenchyma incised, and suture ligate
  - transected blood vessels on renal surface secured w/ figure-of-eight 4-0 chromics
    - hyperinflate lungs to increase CVP → detects unsecured veins
  - collecting system closed w/ interrupted or continuous 4-0 chromics
- **send frozen section to confirm absence of malignancy**
- closure of kidney → 2 ways:
  - approximate transected cortical margins w/ simple interrupted 3-0 chromics
    - place Surgicel at base of defect
  - perirenal fat inserted into base of renal defect, sutured w/ 4-0 chromic
- nephropexy: fix kidney to psoas w/ 3-0 chromics
- retroperitoneal drain x 7days
- ureteral stent
- Post-op follow up
  - Cr, IVP/US in 4-6 weeks
  - surveillance: Hx, Px, Ca, ALP, LFT, BUN, Cr, lytes yearly

## Chapter 102 Questions - Kidney surgery.doc

→ 24h urine in pts w/ partial in solitary kidney

### How does one perform partial nephrectomy for central tumour?

- **complete delineation of renal vascular supply pre-op → CT-angiogram**
- temporary occlusion of renal artery and vein
- kidney mobilized within Gerota's
- divide small intrarenal venous branches
- temporary occlusion of small arterial branches to delineate segment supplied
- intraoperative US may be used
- tumour removed, kidney closed

### What are the advantages and disadvantages of extracorporeal partial nephrectomy?

- Advantages
  - optimum exposure
  - bloodless field
  - more precise operation: maximum conservation of renal parenchyma
  - greater protection of kidney from ischemia
- Disadvantages
  - longer OR time
  - vascular and ureteral anastomoses
  - increased risk of temporary and permanent renal failure

### What are the complications of partial nephrectomy?

- Intra-op
  - hemorrhage
  - adjacent organ injury
  - ureteral injury
  - pleural injury
- Postop
  - urinoma
  - delayed bleeding
  - infection
  - pneumo
  - ileus
  - ureteral stricture
- Bleeding
  - treat w/ bedrest, serial Hgb, VS monitoring, transfusions prn, angio if needed
- Infection
- Fistula
  - AV fistula
  - urine fistula
    - usually resolve spontaneously if there is no distal obstruction → IVP or US
    - tx: NT insertion
- Ureteral obstruction
  - due to clot obstruction
  - tx: ureteral stent
- Renal failure
  - in solitary kidney pts w/ partial nephrectomy, 8% require IHD temporarily, 4% permanent
- Hypertension

### What are the RF for urinary fistulae?

- central tumours
- size > 4cm
- need for major reconstruction of collecting system
- extracorporeal surgery

### What are the indications for renal arterial reconstruction?

- RVH
  - pts w/ peripheral complex branch disease
  - failed PTA

## Chapter 102 Questions - Kidney surgery.doc

- renal artery aneurysm:
  - w/ significant htn
  - > 2cm and noncalcified
  - women of childbearing age
- pts w/ atherosclerotic RVH that cannot be medically controlled, or if renal fn threatened by advanced vascular disease
- ischemic nephropathy
  - pts w/ high grade obstruction (>75%) involving entire renal mass

### What are the clues that may suggest a pt has RVH?

- age < 30yrs or > 50yrs
- abrupt onset and short duration of htn
- presence of extrarenal vascular disease
- end-organ damage: LVH, hypertensive retinopathy
- abdominal bruit
- deterioration of renal fn in response to ACEi

### Describe the technique of aortorenal bypass. (ex: R side)

- Pre-op
  - coronary and carotid artery disease screening and correction
  - arteriography: CO<sub>2</sub> angio
  - hydration
  - mannitol
- Procedure
  - exposure of vessels
    - pt supine
    - subcostal incision, open peritoneum
    - Kocherize duodenum, retract liver and GB superiorly
    - expose R renal artery, R renal vein, IVC, aorta
    - open Gerota's laterally: observe kidney for color
  - expose aorta from L renal vein to IMA
  - mobilize and retract IVC laterally
  - expose distal 2/3 of R renal artery
  - measure bypass graft for length
  - perform end-to-side anast of graft to aorta: minimizes time of renal ischemia
    - DeBakey clamp on aorta
    - oval aortotomy made on anterolateral wall of aorta
    - local endarterectomy if needed
    - bypass graft spatulated, 6-0 Prolene placed at each apex
    - anastomosis completed
    - bulldog released to flush fragments of plaque
    - graft distal to clamp irrigated w/ heparin
  - main renal artery mobilized
    - ligated proximally and bulldog placed distally
    - diseased segment excised and sent off
    - bypass brought anterior to IVC
  - distal anastomosis
    - graft trimmed and anast completed end-to-end w/ 6-0 Prolene

### What are the options for repairing saccular aneurysms of the renal artery?

- primary closure
- patch angioplasty

### What are the options for bypass graft material?

- autologous saphenous vein
- autologous hypogastric artery
- **synthetic → only when autologous graft not available**
  - PTFE

### What options for bypass are available other than aortorenal bypass?

## Chapter 102 Questions - Kidney surgery.doc

- hepatorenal bypass
  - preferred option for pts w/ troublesome aorta that require R renal revascularization
  - GB susceptible to ischemia, may necrose if blood supply from R hepatic removed
- splenorenal bypass
  - preferred option for pts w/ troublesome aorta that require L renal revascularization
  - advantages: single vascular anast, autologous vascular graft
- iliorenal bypass
  - used in pts w/ severe aortic atherosclerosis w/ normal iliacs
  - used only when splenorenal, hepatorenal, or thoracic aortorenal bypass not possible
- thoracic aortorenal bypass
  - used in pts w/ significant abdominal aortic atherosclerosis, celiac artery stenosis, and no indication to replace aorta
  - avoids aortic cross clamping, no need for synthetic graft, limited renal ischemia, and thoracic aorta very healthy
- mesenterorenal bypass
  - used in pts w/ enlarged SMA, significant aortic and iliac disease → pts w/ total occlusion of infrarenal aorta
- extracorporeal microvascular branch renal artery reconstruction
  - used in pts w/ intrarenal extension of renovascular disease
  - **contraindication: severe iliac disease that prevents iliac autotransplantation**

### What RF identify pts that are at highest risk from combined aortic and renal operation?

- MI, existing myocardial ischemia or ventricular hypertrophy
- elevated Cr
- diffuse PVD
- revascularization of both renal arteries at time of aortic replacement
  - operative mortality 63% if 3 or more RF present

### Describe the techniques for the following procedures:

- hepatorenal bypass
  - hepatic artery flow can be safely interrupted: plenty of blood from portal system
  - pre-op LFTs
  - interposition saphenous vein graft anastomosed end-to-side w/ common hepatic just past gastroduodenal, then end-to-end to R renal artery
- splenorenal bypass
  - extended L subcostal transperitoneal incision
  - L colon and duodenum reflected medially
  - dissect plane b/w Gerota's and pancreas bluntly
  - L renal vein mobilized and retracted inferiorly to expose L renal artery
  - pancreatic branches ligated
  - splenic artery occluded proximally w/ bulldog, ligated distally w/ 2-0 silk and transected
    - spleen has plenty of collaterals
  - irrigate splenic artery w/ heparin
  - dilate w/ sounds if in spasm
  - direct end-to-end anast to renal artery
- iliorenal bypass
  - performed using ipsilateral iliac
  - midline transperitoneal incision after harvesting long saphenous vein graft
  - colon reflected medially
  - common iliac occluded w/ bulldogs, 20mL dilute heparin released distally
  - oval arteriotomy made, saphenous graft placed
  - release cclx back into leg
  - end-to-end anastomosis of saphenous vein graft to distal disease-free renal artery performed w/ 6-0 sutures
- thoracic aortorenal bypass
  - use descending thoracic aorta as donor site
  - L thoracoabdominal incision below 8<sup>th</sup> rib
  - L colon reflected medially to expose kidney and renal artery
  - descending thoracic aorta exposed above diaphragm and occluded laterally w/ DeBakey clamp
  - aortotomy made, and reversed saphenous vein graft anastomosed end-to-side w/ aorta
  - saphenous vein graft passed alongside aorta through hiatus posterior to pancreas into L retroperitoneum
  - end-to-end anast of vein graft to distal renal artery
- mesenterorenal bypass
  - midline incision, colon/pancreas reflected



## Chapter 102 Questions - Kidney surgery.doc

- dissect b/w pancreas and Gerota's fascia
- SMA palpated from aorta 1-2cm above level of renal arteries
- SMA mobilized 2-3cm beyond its origin
- L renal artery exposed and isolated
- reversed saphenous vein anastomosed end-to-side to lateral aspect of SMA w/ 6-0 Prolene

### What options can be used to prevent GB ischemia in pts undergoing end-to-end anast in hepatorenal bypass?

- L hepatic artery used
- adjunctive cholecystectomy
- end-to-end anast of gastroduodenal and renal artery

### Describe the technique of extracorporeal microvascular branch renal artery reconstruction.

- Pre-op
  - arteriography: define renal arterial anatomy, ensure disease free iliacs, assess hypogastric artery for use as graft
- Procedure
  - anterior subcostal transperitoneal incision + separate LQ transverse semilunar incision, or single midline incision
  - same principles as donor nephrectomy
    - prevent hypotension
    - mannitol
    - minimal manipulation
    - rapid flushing and cooling in ice
  - reconstruction w/ 7-0 or 9-0 sutures
  - use branched autologous graft
    - reconstructed saphenous graft
    - hypogastric artery → several branches
    - inferior epigastric artery
  - extracorporeal reconstruction
- Postop
  - ICU monitoring for CVP, u/o, VS, Hgb, Cr

### What are the results of renal fn from renovascular reconstruction?

- ischemic nephropathy
  - improved 40%
  - stable 45%
  - worse 15%
- hypertension
  - cured 14%
  - improved 63%
  - unchanged 23%

### What are the complications of renovascular reconstruction?

- mortality
  - minimal in young pts w/ fibrous dysplasia, 6-10% in older pts w/ atherosclerosis
- hypertension
  - due to: hypervolemia, vasoconstriction, pain, renal ischemia
  - may promote bleeding
  - may persist for weeks postop
- bleeding
  - from poor surgical technique (tension, diseased vessels, widely spaced sutures), poor surgical hemostasis (unsecured collaterals in hilum, damage to L adrenal, lumbar)
- renal artery thrombosis: < 5%
  - avoid end-to-end anastomosis of vessels > 50% disparate in diameter
- RAS: < 10%
- RAA
  - graft dilation in 25-50%
  - aneurysm formation in 5-8%
  - seen w/ use of ovarian and gonadal veins for renal bypass surgery → contraindicated
- aortic complications
  - plaque dislodgement → examine lower extremities
- visceral complications

## **Chapter 102 Questions - Kidney surgery.doc**

- splenic laceration: splenectomy
- splenic vein laceration: repair w/ 5-0 Prolene
- pancreatic injury
- hepatic dearterialization: well tolerated
- ischemia of GB: adjunctive cholecystectomy
- intestinal ischemia
- ARF
  - Lasix useful: stimulates release of intrarenal alprostadil (dilates renal afferent arterioles)

### **What policies have been instituted to decrease operative mortality in pts undergoing renovascular reconstruction?**

- screen and correct cerebral and coronary disease
- avoid bilateral renal operations
- avoid operating on badly diseased aorta

### **What factors predispose to renal artery thrombosis post reconstruction?**

- hypovolemia
- hypercoagulable state
- postop hypotension
- intrarenal nephrosclerosis
- intimal flap
- disparate arterial sizes
- graft improperly placed: kinked
- traumatized aorta: embolization of plaque

### **What are the sx of renal artery thrombosis?**

- sudden hypertension
- elevated Cr

### **What are the causes of RAS after reconstruction?**

- damage to vessels during OR
- diffuse subendothelial fibroplastic proliferation
- neointimal proliferation at suture line of synthetic grafts
- recurrent primary vascular disease
- obstruction from valve in segment of saphenous vein
  - saphenous grafts should always be reversed

### **What are the indications for open renal biopsy?**

- solitary kidney
- coagulopathy
- atypical anatomy
- increased risk of closed bx for any other reason
- failed closed bx

### **What are the indications for open NT insertion?**

- difficult anatomy
- minimally dilated upper tract
- concomitant open operation

### **What is Roving's operation?**

- multiple unroofing of renal cysts in PCKD → pain relief



## **Chapter 103**

### **• Laparoscopic Surgery of the Kidney •**

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#### **What is involved in the pre-op workup for laparoscopic renal surgery?**

- informed consent
  - risk of injury
  - risk of conversion to open
- lab and imaging studies
  - ECG, CXR
  - PFTs if known resp disease
- X&T

#### **What are the 3 basic lap approaches to the nephrectomy?**

- transperitoneal
- retroperitoneal
  - preferred in pts w/ multiple previous abdominal surgery, hx peritonitis, abnormality on posterior surface of kidney
- hand-assisted
  - helpful in pts w/ condition that makes lap surgery more difficult: infection, previous surgery
  - requires larger incision than pure lap

#### **What are the indications and contraindications of lap simple nephrectomy?**

- Indications
  - tx of most benign renal diseases w/ loss of renal fn
    - renovascular hypertension
    - ARCD in HD pts
    - nephrosclerosis
    - ADPKD w/ sx
    - chronic pyelo
    - VUR or obstructive nephropathy
    - MCDK
    - post-tx hypertension
- Contraindications
  - Absolute
    - uncorrected coagulopathy
    - untreated infection
    - hypovolemic shock
    - bowel obstruction
  - Relative
    - XGP
    - renal TB
    - obesity
    - previous OR

#### **Describe the procedure of lap simple nephrectomy.**

- Positioning
  - NG, Foley
  - place umbo over break in table
  - modified flank position, axillary roll, flex, tape
- Insufflation and trocar placement
  - insufflation w/ Veress needle
  - thin pts
    - camera port: 10mm in umbilicus
    - working port: 12mm at umbilicus level, lateral to edge of rectus

### Chapter 103 Questions - Lap renal OR.doc

- 5mm port in midline b/w umbilicus and xiphoid
- obese pts (most pts)
  - camera port: 10mm lateral to edge of rectus at umbilicus
  - 12mm port lateral to camera port
  - 5mm port lateral to edge of rectus under costal margin
  - may place 4th 5mm port more superiorly towards midline for liver retraction
- Procedure
  - reflection of colon: incise white line of Toldt from level of iliac to above the spleen
    - incise lienocolic ligament on L
    - incise peritoneal incision above hepatic flexure on R
    - medial traction on liver shows colorenal attachments that must be divided
  - dissection of the ureter
    - identify gonadal vessels and sweep medially
    - identify ureter and elevate: follow proximally to lower pole
  - identification of renal hilum
    - identify vessels entering hilum
    - clip and divide gonadal and lumbar branches
    - place lateral grasper under ureter and kidney until abuts abdominal sidewall
  - securing renal blood vessels
    - gentle dissection w/ tip of irrigation
    - identify renal artery, divide: GIA, Hemolocks
  - isolation of upper pole
    - incise Gerota's fascia anteriorly above hilum, peel off upper kidney
    - preserve adrenal gland
  - organ entrapment
    - kidney removed through morcellation or intact removal
- Post-op
  - remove NG

### What are the results from lap simple nephrectomy?

- postop pain 4X less
- LOS decreases by 50%
- return to work much faster

### What are the advantages of living kidney donation?

- improved graft survival
  - 93% at 1 yr
  - 84% at 5 yr
- less cold ischemic time
- reduced immune suppression requirements
- optimization of both recipient and donor's medical status

### What are the outcomes for lap donor nephrectomy?

- Donor
  - decreased blood loss, readmission rates, time to eating, analgesic requirements, LOS, time to return to work
  - 2% conversion rate, similar complication rates
- Recipient
  - immediate graft function and long-term survival similar b/w lap and open
  - mean serum Cr higher in lap group up to 1 month after transplant
  - same long-term graft survival

### What are the complications of perc renal biopsy?

- significant hemorrhage: 5%
- inadequate tissue: 5-20%

### What are the indications for renal biopsy under direct vision?

- failed perc bx
- anatomic variations
- high risk of bleeding
- unsuitable for perc biopsy

## **Chapter 103 Questions - Lap renal OR.doc**

- morbid obesity
- multiple bilateral cysts
- body habitus
- solitary kidney

### **Describe the technique of lap renal biopsy.**

- position: full flank, umbilicus over break, table fully flexed
- access
  - 10mm transverse incision in skin midway b/w iliac crest and tip of 12th rib in posterior axillary line
  - Optiview port placed, insufflate at 20mmHg
  - blunt dissection w/ laparoscope used to create a retroperitoneal working space
  - anteriorly, peritoneum swept medially, exposing underside of transversalis
  - 5mm port placed in anterior axillary line at same level of 1st port
- kidney exposure and bx
  - may use lap US
  - sweep off fat, 5mm biopsy forcep used
- hemostasis and closure
  - argon beam coagulator → must have vent open
  - Surgicel packed into biopsy site w/ direct pressure
- Postop
  - resume Coumadin 1-2d later

### **What are the results from lap renal biopsy?**

- 100% success in obtaining adequate tissue
- complications in 10%: conversion, bleeding

### **What are the indications for treatment of renal cystic disease?**

- obstruction of collecting system → obstructive uropathy
- compression of renal parenchyma
- hemorrhage: pain and hematuria
- infection
- hypertension
- pain relief: decortication works in 83%

### **What are the important considerations in lap exploration of renal cysts?**

- if cyst close to collecting system, place ureteric stent to identify
  - can instill methylene blue to assess integrity of collecting system
- drain usually not required
- need to drain > 100 cysts to relieve pain in ADPKD

### **What is nephroptosis, and how is it diagnosed?**

- inferior displacement of kidney by > 5cm when pt moves from supine to erect position causing pain in abdomen or flank
  - can cause Dietl's crisis: pain, N/V, tachycardia, oliguria, transient hematuria
- usually in young thin females
- erect and supine IVP or renal scan documenting obstruction
  - descent of kidney by 2 vertebral bodies or diminished flow

### **Describe the technique of lap nephropexy.**

- 3 port configuration
- kidney fully mobilized
- expose fascia over psoas muscle
- place in extreme head down position
- suture lateral edge of capsule of kidney to fascia overlying quadratus
- supine and erect Xrays 6-8 weeks after repair

### **What are the results for nephropexy for documented nephroptosis?**

- 80% improvement in pain

### **What are the indications for lap pyelolithotomy?**

- failed ESWL

### **Chapter 103 Questions - Lap renal OR.doc**

- unusual anatomy: pelvic kidney
- stones resistant to fragmentation: cysteine

#### **What are the indications for lap calyceal diverticulectomy?**

- large peripheral diverticula
- diverticula located medially near renal hilum

#### **Describe the technique of lap calyceal diverticulectomy.**

- Gerota's opened and perirenal fat cleared from kidney
- identify diverticulum: dense adhesions from surface of kidney to surrounding fat
- open thin parenchyma over cavity
- remove stones
- open neck of diverticulum
- fulgurate lining of cavity
- close collecting system

#### **What is the risk of port site seeding in laparoscopy for renal malignancy?**

- minimal
  - TCC: 5 reports
  - RCC: 2 reports

#### **What steps can be taken to prevent port site seeding and tumour spillage?**

- minimize handling of the tissue
- prevent violation of the tumour
- perform wide en bloc resection to get adequate margin
- entrap all cancerous tissue in sac
- remove all potentially contaminated instruments
- send ascitic fluid for cytology

#### **What are the contraindications to lap radical nephrectomy?**

- renal vein or IVC thrombus
- locally advanced disease

#### **Describe the technique of lap radical nephrectomy.**

- Preop
  - metastatic evaluation: CXR, CT, bone scan (if increased Ca/ALP or bone pain)
  - MR to evaluate thrombus
  - renal function: Cr, CT, renal scan if equivocal, 24h CrCl
- Positioning
  - NG, Foley
  - place umbo over break in table
  - modified flank position, axillary roll, flex, tape
- Insufflation and trocar placement
  - insufflation w/ Veress needle
  - thin pts
    - camera port: 10mm in umbilicus
    - working port: 12mm at umbilicus level, lateral to edge of rectus
    - 5mm port in midline b/w umbilicus and xiphoid
  - obese pts (most pts)
    - camera port: 10mm lateral to edge of rectus at umbilicus
    - 12mm port lateral to camera port
    - 5mm port lateral to edge of rectus under costal margin
    - may place 4th 5mm port more superiorly towards midline for liver retraction
- Procedure
  - reflection of colon: incise white line of Toldt from level of iliac to above the spleen
    - incise lienocolic ligament on L
    - incise peritoneal incision above hepatic flexure on R
    - medial traction on liver shows colorenal attachments that must be divided
  - dissection of the ureter
    - identify gonadal vessels and sweep medially

### **Chapter 103 Questions - Lap renal OR.doc**

- identify ureter and elevate: follow proximally to lower pole
- mobilization of lower pole
  - preserve Gerota's fascia
  - lift kidney and dissect to posterior abdominal wall
- identification of renal hilum
  - identify vessels entering hilum
  - clip and divide gonadal and lumbar branches
- securing renal blood vessels
  - gentle dissection w/ tip of irrigation
  - identify renal artery, divide: GIA, Hemolocks
- dissect upper pole
  - if adrenal not removed, incise upper and lateral attachments to Gerota's
  - if adrenal removed, control and divide adrenal vein
- organ entrapment
  - kidney removed through morcellation or intact removal
- Post-op
  - remove NG

### **What are the results from lap radical nephrectomy?**

- cancer free survival 99% at 1 yr, 97% at 5yrs, 83% at 7 yrs
- 8% RCC recurrence rate
- less morbid than open nephrectomy
- comparable cancer free survival

### **What are the challenges associated w/ lap partial nephrectomy?**

- lap control of bleeding difficult
- hypothermia difficult to obtain laparoscopically
- difficult to close collecting system

### **What techniques have been used to control bleeding in lap partial nephrectomy?**

- electrocautery
- Cavitron ultrasonic surgical aspirator
- endovascular GIA stapler
- argon beam coagulator
- topical agents: glue, fibrin
- US energy
- microwave thermotherapy
- cable tie compression

### **What are the complications of lap renal surgery?**

- Access related problems
  - organ injury
  - bowel injury
  - abdominal wall hematoma
  - epigastric vessel injury
- Volume overload
- incisional hernia
- thigh numbness
- ileus
- PE
- pneumonia
- brachial nerve injury
- conversion to open: 10%

### **What is the major cause for conversion to open?**

- bleeding
- inability to visualize hilum



## **Chapter 104**

### **• Other Applications of Laparoscopic Surgery •**

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#### **What are the indications for lap PLND before planned definitive therapy?**

- clinical stage T2b to T3a CaP
- PSA > 20
- Gleason 7-10
- T3c disease
- +ve TRUS/bx after radiation

#### **Describe the technique of transperitoneal laparoscopic PLND.**

- Preop preparation
  - informed consent
  - PO laxatives 1d prior
  - antibiotics
  - Foley, NG
- Positioning
  - supine, arms tucked
- Creation of working space
  - insert Veress needle or perform open access
  - insufflate to 20mmHg
  - inspect peritoneum completely
- LND
  - identify obliterated umbilical ligament, testicular vessels traversing internal ring, external iliac artery
  - initial incision through posterior peritoneal membrane just lateral to obliterated umbilical, extended down just medial to pulsating external iliac artery down toward bifurcation of common iliac to ureter
  - isolate and transect vas
  - clear external iliac vein
  - sweep tissue below external iliac vein off pelvic sidewall
  - LN packet stripped proximally and removed

#### **Describe the technique of extraperitoneal laparoscopic PLND.**

- Creation of working space
  - 2cm infraumbilical midline incision to fascia, stay sutures placed
  - Hasson cannula inserted, CO2 insufflated
  - 3 working ports
- iliac vessels already often exposed
- vas already pushed cephalad, not divided

#### **What are the indications for extended LPLND?**

- bladder cancer, penile cancer, urethral cancer

#### **What are the indications for lap RPLND?**

- clinical stage I NSGCT
- -ve markers
- candidate otherwise considered for surveillance
- no contraindications for lap surgery
- ?residual post-chemo mass

#### **Describe the technique of laparoscopic RPLND.**

- Preop preparation
  - informed consent
  - preop sperm banking



## Chapter 104 Questions - Other lap OR.doc

- bowel prep
- CF only 1d prior
- IV antibiotics
- pneumatic boots
- Positioning
  - modified lateral position, w/ beanbag
  - NG, Foley
  - ureteral catheter
- Transperitoneal approach
  - access w/ Veress needle: ipsi UQ below costal margin
  - pneumoperitoneum created to 20mmHg
  - all 4 ports placed along midline: lower port used to retract bowel medially
- R-sided laparoscopic RPLND
  - creation of the working space
    - surgical table rotated to bring pt into full flank
    - mobilize ascending colon around hepatic flexure
    - peritoneal incision extended laterally around liver towards triangular ligaments to retract liver upward and medially
  - dissection of testicular vessels
    - testicular vessels isolated just above ring
    - stump of cord dissected
    - clip vas medial to external iliac
    - identify proximal ureter as testicular vessels cross
    - clip testicular vessels
    - place testicular vascular remnants in Endocatch bag
  - para- and pre-caval dissection
    - dissect along anterior IVC
    - identify R renal vessels
    - divide fibrolymphatic packages
    - retract IVC medially, dissect to bifurcation
  - interaortocaval dissection
    - clip and transect necessary lumbar veins
    - extend dissection to IMA
    - dissect on medial side of aorta over IVC and along R common iliac
  - hemostasis, remove ports, close

### What have the results been for lap RPLND wrt OR times, hospital stay, and cancer control?

- OR time 5-6hrs
- no local recurrence or port seeding
- overall success 91%
- vascular injury most common cause for conversion

### Describe the technique of lap varicocelectomy.

- GA, NG, Foley, pt prepped
- 3 transperitoneal ports
  - inferior umbilicus camera port
  - 2 5mm ports in each lower quadrant just below umbilicus and lateral to rectus
- 3-5cm incision through posterior peritoneum lateral and parallel to testicular vessels
- 2<sup>nd</sup> perpendicular incision (T incision)
- spermatic cord mobilized
- artery identified w/ lap Doppler probe, veins clipped

### What is the recurrence rate after lap varicocelectomy?

- 1-2%

### What are the indications and contraindications of lap SV dissection?

- Indications
  - lap excision of benign SV cysts
  - w/ lap RP
- Contraindications

## **Chapter 104 Questions - Other lap OR.doc**

- previous SV surgery
- multiple prior abdominal surgery
- radiation hx

### **Describe the technique of lap SV dissection.**

- preop: enema, pt supine w/ Trendelenberg, Foley
- insufflate abdomen open or closed
- 4 trocars placed as per lap PLND
- make transverse incision of peritoneum over rectovesical pouch
- dissect peritoneum bluntly off underlying tissue to expose ampullae of vasa in midline
- isolate, clip, divide each ampulla
- expose underlying SV

### **What are the indications and contraindications of lap RP?**

- Indications
  - same as w/ open RP
- Contraindications
  - **absolute: prior open prostate surgery**
  - previous abdominal surgery
  - previous SV surgery
  - prior TURP
  - hx pelvic rads
  - multiple prostate biopsies

### **Describe the technique of laparoscopic RP.**

- preop: enema, pt supine w/ Trendelenberg, Foley, legs in low lithotomy
- 5 trocars placed: umbilicus (camera), 2 inside rectus below umbilicus, 2 outside rectus below others
- divide vas, mobilize SV, dissect prostate off rectum distally
- develop space of Retzius by dividing urachus and staying medial to umbilical ligaments
- incise endopelvic bilaterally, bluntly remove all levator attachments
- 2-0 passed b/w urethra and dorsal complex and tied
- BN opened anteriorly, catheter removed, posterior margin of BN separated from prostate to expose SV
- divide pedicles
- dissect prostate from NVB
- dorsal vein divided to expose urethra
- remove Foley, divide urethra
- divide rectourethral muscle and remaining attachments
- tennis racquet closure of BN
- vesicourethral anastomosis over Foley
- suction drain, close

### **What are the +ve surgical margin rates in lap vs. open RP?**

- similar: 15-30%

### **What are the contraindications to laparoscopic lymphocele ablation?**

- lymphoceles lateral and posterior or inferior to transplant
- hx of multiple transperitoneal abdominal surgery

### **Describe the technique of laparoscopic lymphocele ablation.**

- supine, Trendelenberg, Foley
- insufflation: open vs. closed
- 3 trocars: 10mm at umbilicus, 5mm in MCL bilaterally at umbilicus
- localize lymphocele: blue bulge in peritoneum
- 3-4cm window made into peritoneum
- tack omentum into window

### **What are the complications of lap lymphocele ablation?**

- GU injury
- transplant injury
- bowel injury

## **Chapter 104 Questions - Other lap OR.doc**

**What are the success rates of lap lymphocele ablation?**

- 6% recurrence